Short Communication

Generative artificial intelligence: In the search for new landscapes in basic and clinical nephrology

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The rise of systems biology has improved the understanding of complex disorders such as chronic kidney disease by providing predictive and comprehensive models. Despite the abundance of omics data, translation to clinical solutions remains a challenge. Artificial intelligence (AI), especially generative AI, promises to fill this gap through mining, integration, and processing of diverse and intricate raw data for the generation of actionable knowledge. Recently introduced AI tools have shown great potential in clinical nephrology for improved diagnosis and prognosis. This approach is also promising for the identification of novel therapeutic targets, repurposing of already approved drugs, and precision nephrology. The rapid advancement of this technology is definitely associated with critical ethical and legal concerns for which the scientific community needs to be prepared.

Key words: Artificial intelligence, diabetic kidney disease, drug repositioning, drug target identification, kidney diseases

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The emergence of systems biology has deepened the comprehension of complex disorders by creating inclusive representations and constructing quantitative predictive models. The explosive generation of big data has fueled the progression of this novel paradigm and allowed for data-driven research for deciphering previously unrecognized molecular mechanisms. However, despite the vast amounts of available omics data, the power of data analysis stays behind data generation. Hence, the translation of such data into clinically relevant solutions remains sub-optimal.[1] Addressing the "big data to knowledge" challenge can provide deeper insights into complex disorders such as chronic kidney disease (CKD). This is important as CKD, including diabetic kidney disease (DKD), is associated with significant morbidity and mortality. Utilizing high-dimensional computational tools for early detection and enhanced treatment of this disorder can have an imperative clinical translational impact. Here, we discuss the emerging field of artificial intelligence (AI) and its competence in improving the management of complex diseases [Figure 1].

ARTIFICIAL INTELLIGENCE: PIONEERING ADVANCES IN BIOMEDICAL RESEARCH

AI refers to the ability of machines to replicate or enhance human intellect, such as reasoning and learning. Generative AI is a type of technology capable of generating various kinds of content that holds immense potential for bridging the gap between data and knowledge, leading to groundbreaking innovations. A representative example is the proficiency of AI to approach the long-lasting problem of forecasting the structure of proteins from their sequences. Although it has been expected for a long time that protein sequences contain all the required data for the formation of three-dimensional structures, this hidden information could not be unlocked until the recent appearance of the AI-based AlphaFold tool and language model-based predictors.[2,3]

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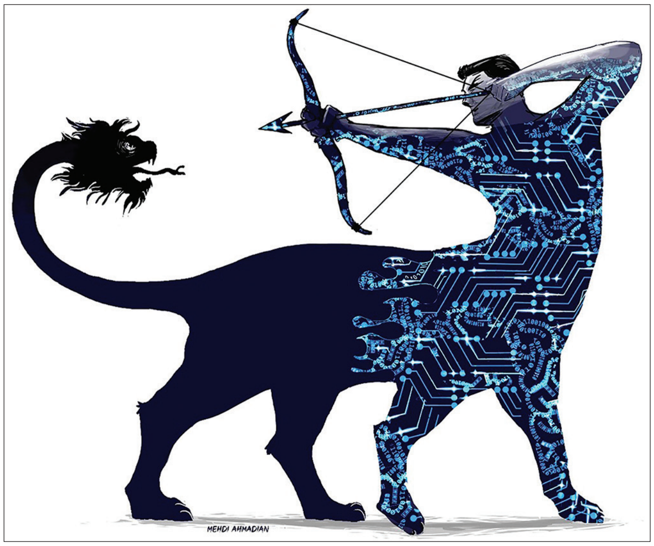

Figure 1: Artificial intelligence (AI) empowers humankind to combat diseases. This illustration takes inspiration from Isfahan City's historical symbol, which depicts the eternal struggle between Good and Evil. The figure represents the potential of AI to empower humanity in the fight against diseases, reflecting the ongoing efforts to utilize AI's capabilities in analyzing medical data, identifying disease trends, and developing new treatment strategies

In various fields of biomedical sciences, such as drug repositioning and drug target identification, vast amounts of data are available. However, achieving the desired insights necessitates sophisticated analysis. AI possesses significant capabilities to uncover hidden knowledge within this wealth of biomedical data. It is believed that the existing data on the structure, targets, and side effects of drugs, as well as disease-associated proteins and processes, is sufficient to propose novel applications for the approved drugs, a dilemma to be fittingly approached by AI.[4] Another instance is the inquiry into protein druggability; the fact that only a minority of proteins are targeted by approved drugs suggests that certain proteins possess a higher tendency to be targeted.[5] Despite initial studies that attributed this tendency to a few characteristics, such as particular topology parameters in the interaction map of proteins,[6] it is now widely accepted that no small set of features can satisfactorily be exploited to predict the druggability of proteins. This aligns with our study demonstrating the high performance of a machine-learning strategy for druggability prediction that considers high-level interactions of numerous protein features.[7] Similarly, we have recently developed "DrugTar," a deep learning based online tool that combines pretrained protein sequence embeddings with protein ontologies to predict druggability of proteins.[8] These algorithms enable researchers to narrow their focus to a limited subset of proteins, selected from the vast array involved in pathogenic mechanisms, as potential therapeutic targets in preclinical experiments, thereby streamlining and accelerating drug development pipelines.

The promise of AI to expedite biomedical science extends beyond its data analysis power and includes data mining as well. Generative AI, including Generative Pre-trained Transformer (GPT), which possesses exceptional natural language processing capabilities, can provide a fitting platform for data mining.[9] However, currently it is not able to utilize the wide spectrum of biomedical data as input. Furthermore, GPT can provide users with data extraction and processing codes, but it is not yet an executable tool. However, the emergence of DrugGPT for de novo drug design and ProGen for the generation of novel protein sequences with predictive functionality illustrates the promise of generative AI models for executable tasks.[10,11] Harnessing the potential of generative AI models, we have recently developed "DrugGen," an online tool that utilizes an enhanced transformer-based generative model to generate valid small molecules with superior binding affinities and docking performance.[12]

The ultimate goal of generative AI in biomedical sciences is to create tools capable of self-optimization to perform complex procedures. In this regard, it is necessary to introduce standards for the availability of biomedical data, such as omics data, to be utilizable by generative AI algorithms. At the same time, these advances highlight the need for proper labeling and curation of training datasets for AI and machine learning methods. Both AlphaFold and GPT were trained using enormous community effort, which was a major and often underestimated prerequisite to their accuracy. With the growing amount of new knowledge, the process of introducing it to the AI models should be considered. A recent example of a mislabeled monkeypox dataset demonstrates the challenges of applying highly automated and complex workflows to large biomedical data.[13] This is especially important as conclusions drawn across data types and physiological scales are difficult to verify.

Moving forward, the integration of heterogeneous big data is a major challenge that can be appropriately approached by deep learning methods. It is increasingly appreciated that phenotypes are the consequence of the interactions between various types of biomolecules. Hence, it is critical to simultaneously inspect the alterations of different layers, such as epigenome, transcriptome, proteome, and metabolome, to generate holistic perspectives of complex disorders.[14] However, the interactions between heterogeneous layers are largely unknown. We have recently developed an algorithm based on deep matrix factorization for link prediction in multi-layer networks,[15] showing the potential of AI for the construction of inclusive maps through large-scale data fusion. A scheme of AI applications in biomedical sciences is depicted in Figure 2.

Considering the above-mentioned capabilities of AI in data mining, integration, and processing, we are currently

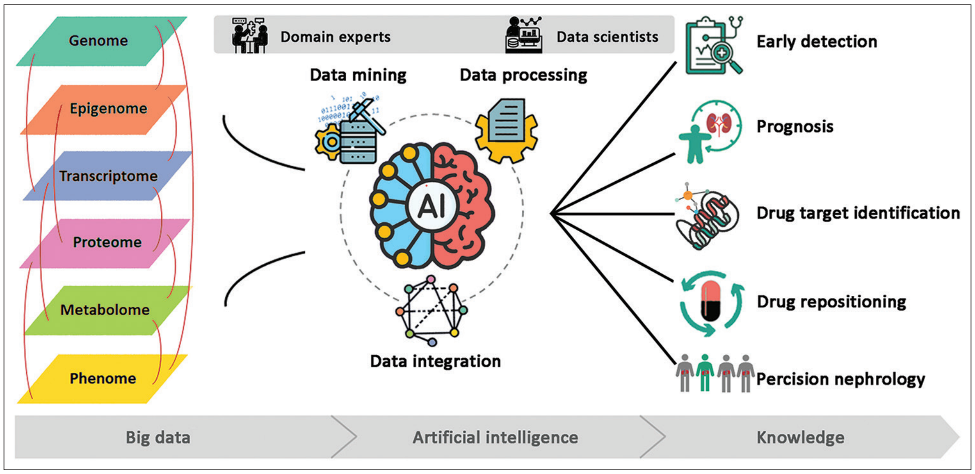

Figure 2: Artificial intelligence (AI): Transforming raw big data into actionable knowledge. AI can be applied to retrieve, integrate, and analyze big data from various layers to generate actionable knowledge. The interdisciplinary collaborations of data scientists and domain experts are at the cornerstone of this process

working to develop a comprehensive executable map for DKD, as a part of the Disease Map Community.[16] In this work, various types of data are retrieved from either literature or omics databases to identify key biomolecules. A holistic multilayer map of interactions can then be constructed that provides a basis for the construction of large-scale dynamic models,[17] drug target identification, and drug repurposing. The outcome can be scientifically and clinically significant given the high incidence of DKD and the paucity of effective drugs for treatment and prevention.

THE PROMISE OF ARTIFICIAL INTELLIGENCE IN BASIC AND CLINICAL NEPHROLOGY

CKD is a major worldwide health problem, currently ranking as one of the leading causes of mortality.[18] Therefore, enhancing the current management strategies is of the highest priority. The recent advent of AI-driven tools for this purpose serves as proof of the capacity of AI to improve the care of multifaceted diseases.

The guidelines for diagnosing CKD primarily rely on serum creatinine and urine albumin levels. However, these markers are not optimal for early detection, as pathogenic disorders often commence long before these indicators can diagnose the disease. Despite concerted efforts, ideal alternative biomarkers for early diagnosis have not yet been introduced. Recently, a few AI-based tools have been developed to process diverse clinical data for early detection and prediction of disease progression.

Retinal assessment has emerged as a valuable screening method for kidney disease, owing to the established link between retinal damage and an elevated risk of CKD. This could be due to the shared physiological and pathological characteristics of the retina and kidney in terms of the microvasculature.[19] In the pursuit of early detection of CKD among the general population and those with diabetes, “RetiKid” and “Reti-Kid-Diab” have been developed, respectively. Impressively, even in the absence of additional information, such as risk factors or laboratory data, these deep-learning algorithms have demonstrated reasonable performance solely based on retinal images.[19,20]

Predicting kidney function from kidney ultrasound and computed tomography (CT) data is an interesting field of research. Using ultrasound images, an innovative study employed a machine learning approach called a convolutional neural network (CNN) to predict the glomerular filtration rate and determine CKD status. The algorithm showed superior performance in diagnosing CKD through kidney ultrasound images compared to experienced nephrologists.[21] Furthermore, a recent study leveraged contrast-enhanced CT images and two deep-learning algorithms to develop a fully automated segmentation tool for multiple kidney structures. The findings established a valuable association between macrostructural segmentation information and microstructural information obtained from biopsy.[22] Such investigations underscore the capacity of AI-based tools to replace invasive diagnostic procedures.

Aside from diagnostic applications, AI algorithms can also be used to predict clinical outcomes. Although glomerulosclerosis is an essential indicator of kidney transplantation outcome, variability in histopathological assessments remains challenging. A recent study utilized a pretrained CNN algorithm to segment and classify normal and sclerotic glomeruli in frozen kidney sections. The algorithm’s performance was comparable to that of professional pathologists, indicating its proficiency to be considered a standard evaluation during the transplantation process.[23]

In addition to clinical images, Electronic Health Records (EHRs) can improve kidney disease management.

The “KidneyIntelX™” is a prognostic AI-based tool that relies on EHR and plasma biomarkers to generate a risk score for kidney function decline in adults with early-stage DKD. This tool was shown to surpass “Kidney Disease: Improving Global Outcomes” risk strata, enabling clinicians to identify individuals at higher risk of rapid disease progression and allowing for timely management to reduce disease complications and enhance patients’ lifestyle.[24] The Food and Drug Administration has granted marketing authorization for this tool.

Besides diagnostic applications and introducing novel therapeutic strategies, AI has the potential to reshape the landscape of precision nephrology. The current therapeutic options for DKD include renin angiotensin system blockers, sodium-glucose co-transporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, and nonsteroidal mineralocorticoid receptor antagonists. It is well expected that the number of these pillars of therapy will increase in the near future, and each patient may best benefit from a specific combination of drugs. Deep learning algorithms could be used to tailor treatments based on each patient’s unique profile.

ETHICAL AND LEGAL CONSIDERATIONS

Along with advancements in AI technology, it is also imperative to enhance the legal and ethical frameworks. In the context of kidney studies, AI can be used to process clinical and paraclinical information, offering opportunities for optimizing clinical procedures and positively impacting medical care. However, it is essential to consider the potential risks and challenges associated with AI technology. Artificial general intelligence aims to construct smart machines that can mimic or even outperform the complex perceptions and thinking of humans. Hence, the access of these algorithms to clinical and biomedical data should be cautiously permitted. Indeed, allowing an intelligent entity equipped with significant computing capabilities to reach an extensive volume of critical data may lead to unforeseen consequences. Moreover, with the advancement of AI technology, its role as an inert tool being used by the operator will be changed to a genuine entity interacting with humans. Should ownership rules be revisited to consider this type of contribution? What about responsibilities? In a situation where an AI proposes a patient management approach, who bears the liability for any incorrect decision-making? Such apprehensions underscore the importance of creating ethical and legal frameworks that correspond with the high capabilities and rapid growth of this technology.

CONCLUDING REMARKS

The high capacity of AI to retrieve, integrate, and process huge amounts of biological and clinical data holds immense promise to shape novel landscapes. The scientific community needs to plan for significant adaptations, from changing data deposition standards to rewiring ethical and legal frameworks to prepare for this game-changing technology.

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Conflicts of interest

There are no conflicts of interest.

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