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ARTIFICIAL INTELLIGENCE FOR DRUG TOXICITY AND SAFETY

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ABSTRACT

Artificial intelligence (AI) has significantly contributed to advancements in biomedical sciences; however, its impact on regulatory science remains limited. With continuous progress in drug development, in silico and in vitro approaches are increasingly explored as alternatives to animal studies to identify and mitigate safety concerns at earlier stages. Despite the availability of numerous AI-based tools, their acceptance in regulatory decision-making for drug efficacy and safety evaluation continues to be challenging.

It is commonly believed that AI models improve with the availability of larger datasets, but this assumption may not always hold true in drug safety assessments. For regulatory applications, AI models must consider multiple characteristics, including adaptability, which refers to a model's ability to adjust its performance when retrained on new and unseen data. Adaptability is a critical factor that should be evaluated before implementing AI models in regulatory frameworks.

In this study, we conducted a comprehensive assessment of model adaptability by simulating real-world conditions, including the annual introduction of new drugs into the market. We utilized Deep DILI, a previously developed deep learning model for predicting drug-induced liver injury (DILI). Our results demonstrated that the selection of the target test dataset plays a crucial role in evaluating adaptive behaviour. Furthermore, the inclusion of additional drugs in the training dataset did not result in a significant improvement in predictive performance.

Overall, this study highlights the importance of adaptability assessment and suggests that the proposed framework can effectively evaluate the long-term performance and reliability of AI models for regulatory drug safety applications.

KEYWORDS: Artificial Intelligence; Regulatory Science; Drug Safety; Deep Learning; Drug-Induced Liver Injury (DILI); Model Adaptability.

INTRODUCTION

The development of a safe and effective therapeutic agent is a complex, time-consuming, and costly process, with drug safety and toxicity assessment representing one of the most critical determinants of success in pharmaceutical research.

A significant proportion of drug candidates fail during preclinical and clinical phases due to unexpected toxic effects, while some approved drugs are later withdrawn from the market because of serious adverse drug reactions (ADRs). Traditional toxicological evaluation relies heavily on in vitro experiments, animal studies, and clinical trials; although these methods remain the gold standard, they are often expensive, labor-intensive, time-consuming, and sometimes limited in their ability to accurately predict human responses.

In this context, Artificial Intelligence (AI) has emerged as a transformative technology with the potential to revolutionize drug safety assessment and toxicology by enabling faster, more accurate, and data-driven decision-making.

Artificial Intelligence refers to the use of computational algorithms that can learn from data, identify patterns, and make predictions or decisions without being explicitly programmed for each task. Subfields such as machine learning, deep learning, natural language processing, and neural networks are increasingly being applied across the pharmaceutical and biomedical domains. In drug safety and toxicology, AI systems can analyze vast and complex datasets, including chemical structures, biological activity profiles, genomic data, electronic health records, pharmacovigilance databases, and real-world evidence, to predict potential toxic effects at an early stage of drug development.

This capability not only reduces the risk of late-stage drug failure but also minimizes the need for extensive animal testing and lowers overall development costs.

One of the most important applications of AI in toxicology is in silico toxicity prediction. Computational models such as quantitative structure–activity relationship (QSAR) models, when combined with machine learning techniques, can predict the toxic potential of new chemical entities based on their molecular properties.

These models are widely used to assess hepatotoxicity, cardiotoxicity, mutagenicity, carcinogenicity, and reproductive toxicity before a compound enters experimental testing. Early prediction of such toxicities enables researchers to modify or eliminate harmful compounds at the initial stages, thereby improving the efficiency of the drug discovery

pipeline.

In clinical drug safety, AI plays a vital role in pharmacovigilance by enhancing the detection, assessment, and prevention of adverse drug reactions.

Traditional pharmacovigilance methods rely on spontaneous reporting systems, which are often affected by underreporting and delayed signal detection. AI-driven tools can process large volumes of structured and unstructured data from sources such as electronic medical records, clinical trial reports, biomedical literature, and even social media platforms to identify previously unrecognized safety signals in real time.

Natural language processing, in particular, enables automated extraction of relevant safety information from narrative clinical notes and case reports, thereby significantly improving the efficiency and accuracy of ADR monitoring**.**

1.Computational toxicology in drug safety research]

The progress of computational toxicology (CompTox) in drug safety research is highly anticipated. CompTox provides toxicity screening methods for drug discovery in the early stages. CompTox also contributes to fostering the application of the principles of the 3Rs in toxicity testing by expanding non-animal test methods.

The mechanism of toxicity is complex and varied, and drug discovery modalities are becoming more diverse. Consequently, the research is considered necessary to predict toxicity using not only chemical structures but experimental data as well.

Additionally, various perspectives, such as interpretation of toxicity mechanisms and species differences, must be considered in risk assessment and management in drug safety research. Therefore, it is important to construct a comprehensive CompTox system that not only presents toxicity prediction results but also provides much information related to the relationship between drug candidate substances and living organisms.

In this review paper, CompTox is positioned as a discipline of toxicology that applies computer-based technology, including AI (artificial intelligence).

I also introduce toxicity prediction systems based on experimental data and an ontology system that supports the interpretation of toxicity prediction results as examples of research on constructing the foundation of a comprehensive CompTox system.

2. Adaptability of AI for safety evaluation in regulatory science: A case study of drug-induced liver injury:

Artificial intelligence (AI) has played a crucial role in advancing biomedical sciences but has yet to have the impact it merits in regulatory science.

As the field advances, in silico and in vitro approaches have been evaluated as alternatives to animal studies, in a drive to identify and mitigate safety concerns earlier in the drug development process.

Although many AI tools are available, their acceptance in regulatory decision-making for drug efficacy and safety evaluation is still a challenge. It is a common perception that an AI model improves with more data, but does reality reflect this perception in drug safety assessments?

Importantly, a model aiming at regulatory application needs to take a broad range of model characteristics into consideration.

Among them is adaptability, defined as the adaptive behavior of a model as it is retrained on unseen data. This is an important model characteristic which should be considered in regulatory applications. In this study, we set up a comprehensive study to assess adaptability in AI by mimicking the real-world scenario of the annual addition of new drugs to the market, using a model we previously developed known as Deep DILI for predicting drug-induced liver injury (DILI) with a novel Deep Learning method. We found that the target test set plays a major role in assessing the adaptive behavior of our model.

Our findings also indicated that adding more drugs to the training set does not significantly affect the predictive performance of our adaptive model. We concluded that the proposed adaptability assessment framework has utility in the evaluation of the performance of a model over time.

3. Potential Applications of Artificial Intelligence (AI) in Managing Polypharmacy :

Prescribing medications is a fundamental practice in the management of illnesses that necessitates in-depth knowledge of clinical pharmacology. Polypharmacy, or the concurrent use of multiple medications by individuals with complex health conditions, poses significant challenges, including an increased risk of drug interactions and adverse reactions.

The Saudi Vision 2030 prioritises enhancing healthcare quality and safety, including addressing polypharmacy. Artificial intelligence (AI) offers promising tools to optimise medication plans, predict adverse drug reactions and ensure drug safety. This review explores AI's potential to revolutionise polypharmacy management highlighting practical applications, challenges and the path forward for the integration of AI solutions into healthcare practices.

4. Deep Learning-based Modeling for Preclinical Drug Safety Assessment:

In drug development, assessing the toxicity of candidate compounds is crucial for successfully transitioning from preclinical research to early-stage clinical trials. Drug safety is typically assessed using animal models with a manual histopathological examination of tissue sections to characterize the dose-response relationship of the compound - a time-intensive process prone to inter-observer variability and predominantly involving tedious review of cases without abnormalities.

Artificial intelligence (AI) methods in pathology hold promise to accelerate this assessment and enhance reproducibility and objectivity. Here, we introduce TRACE, a model designed for toxicologic liver histopathology assessment capable of tackling a range of diagnostic tasks across multiple scales, including situations where labeled data is limited. TRACE was trained on 15 million histopathology images extracted from 46,734 digitized tissue sections from 157 preclinical studies conducted on Rattus norvegicus. We show that TRACE can perform various downstream toxicology tasks spanning histopathological response assessment, lesion severity scoring, morphological retrieval, and automatic dose-response characterization. In an independent reader study, TRACE was evaluated alongside ten board-certified veterinary pathologists and achieved higher concordance with the consensus opinion than the average of the pathologists.

Our study represents a substantial leap over existing computational models in toxicology by offering the first framework for accelerating and automating toxicological pathology assessment, promoting significant progress with faster, more consistent, and reliable diagnostic processes.

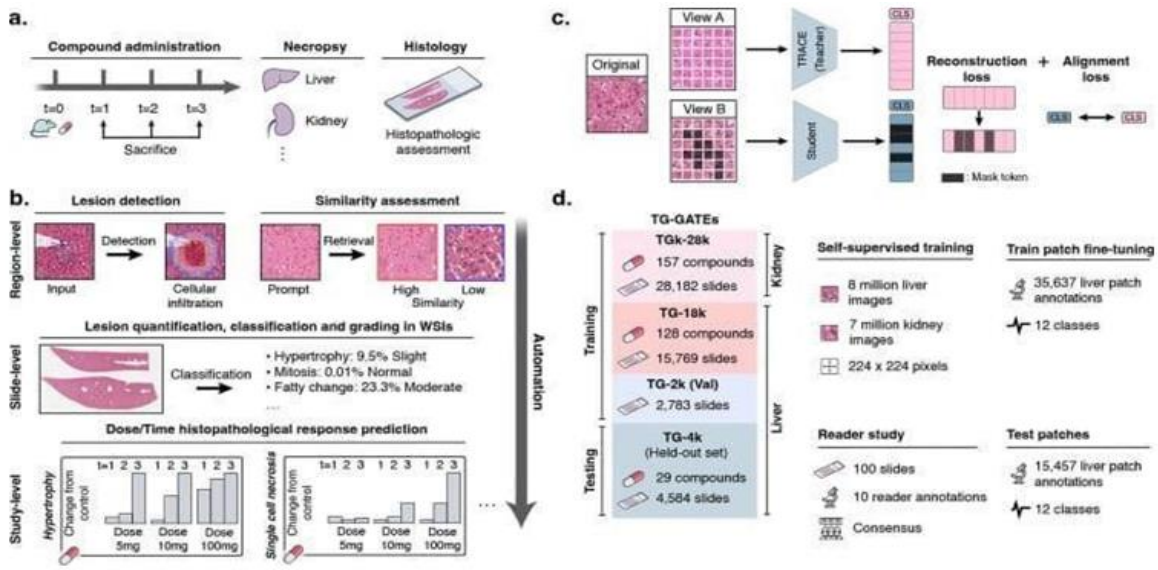

Figure 1: Preclinical AI-enhanced safety assessment. a. Before entering.

human clinical trials, compounds must undergo a preclinical safety assessment on rodents to assess their potential toxicity. b. Preclinical histopathological drug safety studies can benefit from AI assistance and automation at different scales: at region-level to detect and retrieve certain morphologies and lesions, at slide-level to automatically quantify and score abnormal lesions in WSIs, and at study-level to automatically characterize the dose-time morphological response of the candidate compound. c. We train TRACE , a self-supervised vision encoder based on the Vision Transformer architecture trained to extract representative embeddings of small histopathological regions in Rattus norvegicus. TRACE uses iBOT training which combines a contrastive self-distillation objective, and an image reconstruction objective.

5. Computational toxicology in drug discovery: applications of artificial intelligence in ADMET and toxicity prediction:

Toxicity risk assessment plays a crucial role in determining the clinical success and market potential of drug candidates. Traditional animal-based testing is costly, time-consuming, and ethically controversial, which has led to the rapid development of computational toxicology. This review surveys over 20 ADMET prediction platforms, categorizing them into rule/statistical-based methods, machine learning (ML) methods, and graph-based methods. We also summarize major toxicological databases into four types: chemical toxicity, environmental toxicology, alternative toxicology, and biological toxin databases, highlighting their roles in model training and validation.

Furthermore, we review recent advancements in ML and artificial intelligence (AI) applied to toxicity prediction, covering acute toxicity, organ-specific toxicities, and carcinogenicity. The field is transitioning from single-endpoint predictions to multi-endpoint joint modeling, incorporating multimodal features.

We also explore the application of generative modeling techniques and interpretability frameworks to improve the accuracy and credibility of predictions. Additionally, we discuss the use of network toxicology in evaluating the safety of traditional Chinese medicines (TCMs) and the potential of large language models (LLMs) in literature mining, knowledge integration, and molecular toxicity prediction.

Finally, we address current challenges, including data quality, model interpretability, and causal inference, and propose future directions such as multi-omics integration, interpretable AI models, and domain-specific LLMs, aiming to provide more efficient and precise technical support for preclinical toxicity assessments in drug development.

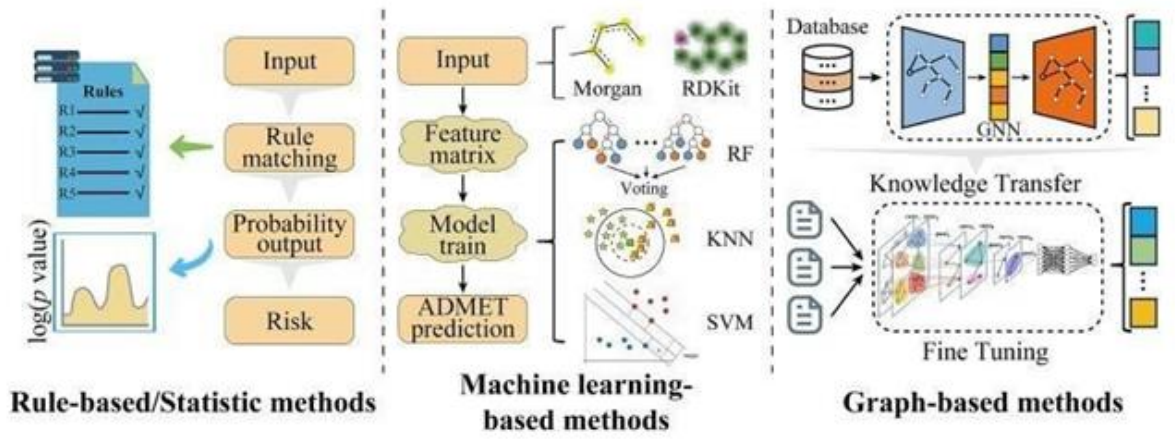

Figure 1: Classification of computational modeling approaches in ADMET prediction platform: rule/statistics based methods, ML based methods, and graph-based methods.

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