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Chapter 11

Recent Advances in AI-Based Toxicity Prediction for Drug Discovery

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Abstract: Toxicity evaluation is a crucial component of drug discovery, as chemical compounds that enhance human health may also pose serious risks. Conventional in vitro and in vivo approaches, while informative, are time-consuming, costly, and dependent on extensive experimentation. The rapid growth of computational approaches and the availability of large experimental datasets have enabled the development of artificial intelligence (AI)–based toxicity prediction models that provide a more efficient strategy for early-stage screening. By integrating public databases such as ChEMBL, Drug Bank, and Binding DB with proprietary in vitro, in vivo, and clinical data, AI models create a feedback loop that improves predictive performance and supports regulatory decision-making. Recent progress in machine learning and deep learning, including Random Forest, Support Vector Machines, Graph Neural Networks, and transformer-based architecture, has demonstrated strong performance in predicting diverse endpoints such as hepatotoxicity, cardiotoxicity, neurotoxicity, and genotoxicity. This article reviews these advances and discusses strategies such as multi-task learning, multimodal integration, and scaffold-based evaluation to address challenges of data heterogeneity, class imbalance, and protocol variability. Despite these developments, issues such as data quality, interpretability, and standardization remain barriers to widespread implementation. Overall, this review emphasizes that AI-based toxicity prediction holds great promise to accelerate drug discovery, reduce attrition, and guide safer therapeutic development.

Keywords: Artificial Intelligence, Machine Learning, Toxicity Prediction, Drug Discovery, Computational Toxicology, Deep Learning, Graph Neural Networks, Regulatory Toxicology.

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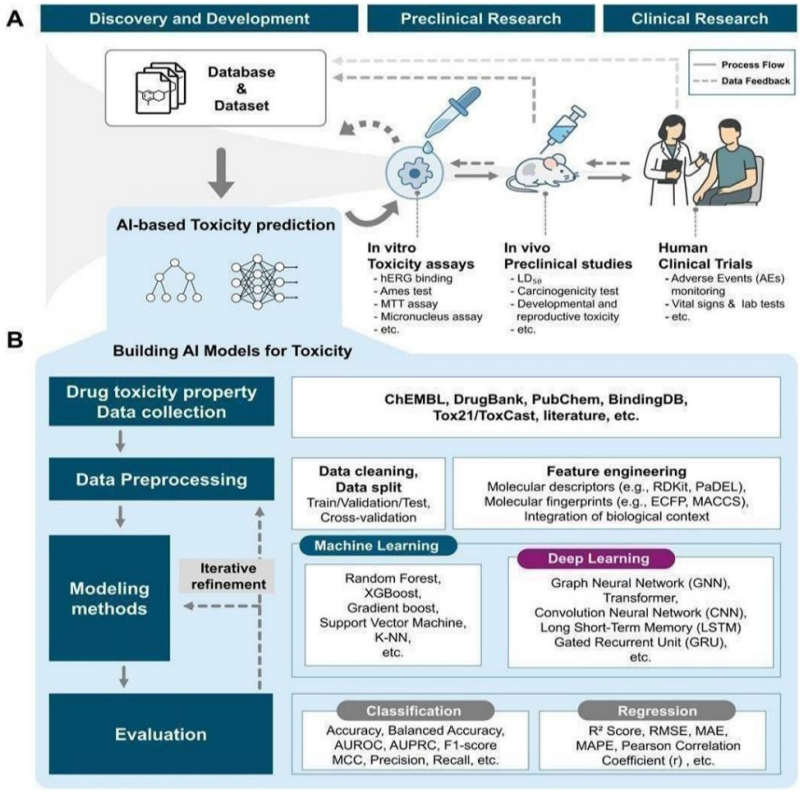
1. INTRODUCTION

Toxicity is defined as how much a substance that can harm living things like animals, plants, bacteria, and people. While many chemicals make our life better, they can also be very dangerous. To keep people safe different sets of rules have been developed to reduce these dangers. Because being exposed to chemicals can be harmful to health, it is important to carefully check these substances in the environment. The rules usually require testing to see how poisonous a substance include finding out what dangers it has, how much is harmful, how people might be exposed, and what overall risk is. As a part of hazard identification. It is important to find out what kind of toxic effects each chemical can cause. At the same time, laboratory studies (both in vitro and in vivo) help to understand the conditions under which these effects might happen in human beings, often using information from human health studies. Does-response assessments look at how the amount of exposure to a chemical is related to harmful effects, using measures like NOAEL, LOAEL and the possibility of causing cancer (NRC, 1994). This method focuses on how much exposure leads to harm the adverse outcome pathway AOP framework adds a mechanistic point of view. An AOP starts with a molecular initiating event-such as a chemical binding to a receptor-and follows a chain of key events that finally lead to an adverse outcome in the organism. By integrating or mixing the mechanistic details with experimental results, AOPs show how different types of data can be combined to better understand chemical toxicity. This growing focus on data integration has also encouraged the use of AI-based models that combine both experimental and computer-generated data to help in predicting toxicity at an early stage.**[1]**



2. OVERVIEW OF AI IN DRUG DISCOVERY

2.1-Evolution of Computational Approaches

The traditional process of discovering new drugs is very long and expensive – it can take up to 15 years and cost between $1 and $2 billion for just one approved drug. This is mainly because of many potential drugs fail during testing, especially in clinical trials. Almost 90% of drug candidates fail even after reaching the first stage of clinical trials. Getting a drug to phase I trials after years of testing in the lab is considered a major success for both companies and research institutions.**[2]**

To increase success rates, scientists have used large-scale computer-based screening and docking methods to test how compounds might interact with biological targets. However, these methods are sometimes slow and not always accurate. To solve this AI and ML – especially Deep Learning are used more. These tools can predict properties of compounds accurately while using less computing power and time. As a result, Artificial Intelligence has become an important part of the modern drug discovery process.**[2]**

Machine learning which uses algorithms such as Deep Learning, Bayesian Networks, Random Forest, Clustering, and Support Vector Machine that are used to study drug data.**[2]**

AI and ML-based modeling are now used for many parts of drug discovery, including predicting drug targets testing drug safety, identifying chemical compounds, checking drug effectiveness, predicting protein behavior, and even finding new uses for old drugs.**[2]**

For example, AlphaFold, developed by Google DeepMind, uses AO to predict protein structures. Machine learning can also be used for virtual screening by training models on knows data and then using those models to find new compounds that may act on a target effectively.**[2]**

2.2-Advantages of Ai Over Traditional Rule - Based Models

AI and ML have brought more changes to drug discovery, which are helping to solve long-standing problems like high cost, slow timelines, and very low success rates**.[3]** Traditional methods can be slow, expensive, and not always accurate. They are often limited to by the number of test compounds and the difficulty of predicting how drugs behave in the human body.**[4]** By analyzing large datasets, ML can identify patterns that human researchers might miss. This helps scientists find promising drug candidates faster and with better accuracy.**[5]**

3. TYPES OF TOXICITY RELEVANT TO DRUG DEVELOPMENT

- HEPATOTOXICITY (LIVER INJURY, DILI PREDICTION)
- CARDIOTOXICITY (HERG INHIBITION, QT PROLONGATION)
- NEUROTOXICITY (CNS-RELATED TOXICITIES)
- GENOTOXICITY & CARCINOGENICITY
- IMMUNOTOXICITY & HYPERSENSITIVITY REACTIONS

3.1-Hepatotoxicity

The liver is the main organ that breaks down drugs and other foreign substances. Since most drugs are taken orally, the liver is the first to process them after absorption form the stomach and intestines. This makes it vulnerable to drug-induced damage. However, only about 9.5% of all ADR's affect the liver.

When liver injury occurs, it is very serious and sometimes may lead to death. For example, the drug halothane can cause liver failure in rare cases, with a fatality rate of about 50%. Other sources of liver toxicity include industrial chemicals, natural toxins, and even some herbal remedies.**[6]**

3.2-Cardiotoxicity

Heart toxicity is a major safety concern in drug development, along with liver and nervous system toxicity. It causes around 27% of drug failures in development. Once of the biggest concerns is drug-induced arrhythmia, especially a server type called Torade de pointes, which can lead to sudden cardiac death. Between 1990 and 2006, about one-third of all drugs withdrawn from the market was due to QT prolongation or Td P risk. Even today, around 15% of marketed drugs can cause QT prolongation, and about 4% are linked to TdP. Therefore, it is very important to identify heart toxicity early to prevent harm and financial loss. **[7]**

3.3-Neurotoxicity

Neurotoxicity refers to damage to the brain and nerves, leading to problems in how they work. This can happen in both the CNS and PNS. Neurotoxicity can involve several mechanisms such as neuron damage, axon damage, or problems with neurotransmission. Even useful drugs also cause neurotoxicity. For instance, vincristine, a cancer drug, may lead to peripheral neuropathy, causing numbness and weakness. Because of such risks, new drugs are tested for neurotoxicity using international test standards such as OECD Test Guidelines 418, 419 and 424. **[8]**

3.4-Genotoxicity & Carcinogenicity

Genotoxicity means damage to a cell's DNA or RNA, which can lead to mutations and sometimes cancer. Substances that cause such effects are called genotoxins, which may be chemicals or radiation. It's important to note that while all mutagens are genotoxic, not all genotoxic substances cause mutations directly. Understanding genotoxicity helps identify cancer-causing risks early in drug testing.**[9]**

3.5-Immunotoxicity & Hypersensitivity Reactions

Adverse immune reactions to drugs can cause serious problems. Drug-induced hypersensitivity occurs when the immune system reacts to a drug given at a normal dose. Such reactions may not be noticed until a drug is widely used. Because more drugs are being linked to immune reactions, testing for hypersensitivity in animals before marketing is now common practice.**[10]**

4. AI APPROACHES FOR TOXICITY PREDICTION

4.1-Machine Learning Models

Machine learning algorithms are widely used to predict drug toxicity, especially liver toxicity. ML classifies chemicals as toxic or non-toxic by learning from data such as chemical structure and know effects. Common ML models used include Naïve Bayes Classified, Support Vector Machines, and Random Forests.**[11]**

4.2-Deep Learning Models.[11]

Deep learning is a type of ML that uses complex neural networks to analyze raw data and find hidden patterns automatically. Dl models can process large datasets and provide accurate predictions of toxicity.

Some commonly used DL models include:

- Multi-Layer Perceptron (MLP)
- Deep Neural Networks (DNN)
- Convolutional neural Networks (CNN)
- Graph Neural Networks (GNN)
- Recurrent Neural Networks (RNN)
- Generative Adversarial Networks (GAN)
- Transformers

4.3-Hybrid & Ensemble Approaches [12]

People are exposed daily to thousands of potentially toxic chemicals – from food, air, medicines, and industrial products. Testing all these using animals' studies is time-consuming, costly, and raises ethical concerns. Because of this, in Silico toxicity testing is becoming popular. ML models can predict whether a substance is toxic, how toxic it might be, or categorize it as high, medium, or low toxicity.

Examples include:

- KNN method: 79% accuracy for predicting acute toxicity
- ANN method: 93% accuracy for predicting antibacterial activity
- SVM and RF models: around 70-80% accuracy for predicting carcinogenicity

These models show how AI can save time and improve accuracy in toxicity prediction.

4.4-Explainable AI

Drug discovery is complex and expensive. AI helps speed up this process by analyzing biological and chemical data more efficiently. However, AI models are often seen as "black boxes", meaning their decisions aren't easily understood. Explainable AI solves this problem by making AI decisions easier to interpret. XAI helps scientists and doctors understand why an AI made a specific prediction, which builds trust and makes validation easier. Companies like Ex Scientia and Benevolent AI have successfully used XAI to speed up drug discovery - cutting development time from year to month.

5. DATA SOURCES & DATABASES FOR TOXICITY PREDICTION

5.1-ADMET Databases

ADMET stands for Absorption, Distribution, Metabolism, Excretion, and Toxicity. These properties are crucial for understanding how a drug behaves in the body. Poor ADMET results often lead to drug failure.

Computational methods now allow early and cheaper ADMET testing. Popular databases and tools include:

- Drug Bank
- ChEMBL
- PKKB
- SwissADME
- ADMETlab2.0
- ProTox-II
- admestSAR

5.2-Toxicogenomic Repositories

The TG-GATEs database stores genetic and toxicity data from rat and human liver cell experiments involving 170 chemicals. It includes data on biochemistry, histopathology, and cytotoxicity. This database was created through a 10-years project in Japan involving government and pharmaceutical companies, helping researchers link gene expression changes to toxic effects.**[15]**

6. EMERGING AI INNOVATIONS IN TOXICITY PREDICTION

Toxicity prediction depends heavily on the quality and amount of available data. When data is limited, special techniques like transfer learning and multi-task learning help improve performance.

Examples include:**[16]**

- Helix ADMET: uses multi-stage training to improve chemical property prediction.
- M2REMAP: combines molecular and clinical data to predict drug side effects more accurately.
- muTOX-AL: uses active learning to pick the most informative samples, reducing the need for large datasets.
- MEELLODDY Project: uses federated learning, allowing multiple companies to train models together without sharing private data.

7. LIMITATIONS

Although AI-based toxicity prediction has improved a lot, challenges still exist. AI sometime struggles to predict rare or complex toxicities because of limited high-quality data.

Other limitations include:

- Difficulty in generalizing results to new chemical types
- Lack of interpretability (how AI planned)
- Limited data reflecting real-world human outcomes

These issues make regulatory acceptance and clinical use more difficult.

8. CHALLENGES AND PROSPECTS

8.1-Expanding Sample Sizes

Small sample sizes reduce model accuracy. However, growing access to genomic and chemical data helps solve this problem. Techniques like data augmentation, active learning, and pretrained models can help build stronger models. Open platforms like CTD and TTD also support data sharing to improve results.**[17]**

8.2-Improving Data Quality and Integrating Diverse Sources

Combining data from different sources is difficult because formats and quality vary. To improve reliability, researchers use standardized cleaning, validation, and integration methods. Advanced techniques like federated learning and multimodal ML help me merge chemical, toxicological, and biological data, resulting in good toxicity prediction. **[17]**

8.3-Enhancing ML Models for Diverse Toxicity Detection

Various types of toxicity such as acute, cancer-causing, or organ-specific work through different biological mechanisms. This means models must be customized for each type of toxicity to ensure accuracy**.[17]**

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