AI-DRIVEN PREDICTIVE TOXICOLOGY FOR EARLY DRUG SAFETY ASSESSMENT

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Abstract : Drug toxicity is one of the most common reasons for failures in drugs, contributing to around 30% of failures in drug discovery and associated with enormous monetary losses and moral issues. Conventional methods of toxicity testing, which are based on animal models, are time-consuming, cost-prohibitive, and associated with several moral issues, while being less predictive for humans. Recent advances in AI and ML tools have brought forth breakthroughs for predicting drug toxicity in the early stages of drug development. AI and ML tools, which are novel for predicting drug toxicity, are discussed in this comprehensive review, which reviews cutting-edge AI methodologies such as quantitative structure-activity relationship, deep neural networks, and graph neural networks. We also discuss core endpoint toxicities such as hepatotoxicity, cardiotoxicity, nephrotoxicity, genotoxicity, carcinogenicity, and reproductive and developmental toxicities. We address core data resources (Tox21, ToxEst, PubChem, and ChEMBL, which are major databases); perspectives from FDA and EMA; issues associated with AI interpretability, and future perspectives, which include digital twin and organ-on-chip technologies. AI-based predictive toxicology, discussed in this comprehensive review, clearly establishes that AI-based predictive models are less time-consuming and better predictive than conventional methods and will soon replace many animal testing processes.

keyword: Artificial intelligence, machine learning, drug toxicity prediction, QSAR, deep learning, computational toxicology, early safety assessment.

Introduction

1.1 Importance of Toxicity in Drug Development One of the most important obstacles to effective pharmaceutical development is drug toxicity. Unexpected toxicity causes about 30% of drug candidates to fail clinical trials, resulting in annual cumulative losses of billions of dollars.[1] [2]. Toxicity failures affect patient safety and postpone access to potentially life-saving treatments, in addition to financial consequences. Strong assessment techniques are required prior to clinical evaluation because drug toxicity in human populations is unpredictable.

1.2 Limitations of Conventional Toxicology Assessment :-

The conventional toxicology is very dependent on in vitro cell-based bioassays and in vivo animal tests. This is even though these technologies have been shown to be major limitations. In vitro models have been proven ineffective in recreating human physiology, biochemistry, and interactions among various organs required in effectively testing the toxicological properties of chemicals [3].In vivo animal tests may be helpful in providing a whole-organism perspective; however, this kind of testing is very costly (taking 6-12 months) and

is also very expensive. Furthermore, it has been shown to have very limited relevance to human toxicology when interspecies variations are taken into consideration. These conventional methodologies also account for massive consumption of chemicals as well as animals. Regulatory bodies have estimated the annual use of millions of animals in toxicological testing worldwide [4] [5].

1.3 Rise of AI and Machine Learning in Toxicology :-

Applications in various research domains have transformed the field of AI, machine learning, and predictive toxicology, and the latter appears to be one of the most promising. The coming together of three main facilitators has catalyzed the incorporation of AI in predictive toxicology: (1) the exponentially increased amount of available public toxicity data generated by high-throughput screening projects such as Tox21 and ToxCast, (2) the rapid progress made in machine learning modeling, especially in the area of deep learning methods, and (3) the increased computing powers and the emergence of various open-source platforms.[6,7] AI-based methods utilize available chemical and toxicological knowledge to develop predictive models to quickly evaluate new compounds, detect structural features related to toxic compounds (toxicophores), and estimate the potential toxicity before the compounds can be manufactured or animal-tested.

1.4 Scope and Organization of Review:-

This review aims at understanding the state-of-the-art in the area of predictive toxicology through the use of artificial intelligence. To ensure clarity and comprehensiveness, we have sectioned our review into several areas, including: (1) the limitations of the conventional approach; (2) the use of artificial intelligence in the field of toxicology; (3) the prediction of certain endpoints of toxicity; (4) its applications in early drug safety evaluation; (5) regulatory aspects; (6) its benefits and challenges; and finally, (7) future outlooks. Throughout the review, we will focus on the revolutionary prospects of artificial intelligence in lowering animal usage and enhancing the precision of prediction in early drug development stages.

2.Conventional Toxicology Methods and their Shortcomings

2.1 In Vitro Toxicity Testing :-

In vitro cytotoxicity tests use cell lines or primary hepatocytes to investigate cell death induced by chemicals based on various endpoints such as viability (MTT, LDH release), apoptosis (caspase activation), and metabolic function. Cell-based assays have advantages in turnaround times (hours to days) with significantly reduced costs relative to animal tests, in addition to allowing mechanistic analysis of toxicity routes [8] .However, in vitro assays have natural inherent weaknesses in being unable to provide plausible tissue structure properties while lacking functionality based upon more than one organ in the body in addition to being susceptible to variability in results according to cells in culture properties.

Limitations and Ethical Issues:-

In vivo studies in animals are widely accepted by regulations, although there are major drawbacks in their processes. Interspecies extrapolations are challenging; toxic compounds in animal studies could be non-toxic in humans and vice versa, which led to certain failed medicines in the past (TGN1412, causing immunotoxicity in humans) [9].

There are certain moral objections concerning the infliction of pain in animal studies, which led to global regulatory change in the 3R concept: “Replace, Reduce, Refine.”[10][11] This is a time- and resource-consuming procedure in which dozens of animals are required (between 20-100 in a single project), as well as a considerable amount of time (typically 6-24 months) and specialized infrastructure in the form of particular bioresearch centers and veterinary staff, as well as adhering to regulations.

3. Introduction to AI in Toxicology: Definitions and Principles

3.1 Definition

Artificial Intelligence (AI) relates to computer systems crafted to execute human-level intelligent tasks like data-driven learning, pattern analysis, and decision-making. In the context of drug discovery and toxicology, AI generally relates to

Machine Learning (ML) includes algorithms that can improve performance at a given task with experience with data rather than following explicitly programmed commands. Machine learning algorithms find patterns within data sets that can potentially be missed by a human and make predictions for unmeasured properties given known chemical structure and outcomes.

Deep Learning (DL) is actually a field of ML involving the use of ANNs comprising multiple layers of hidden layers (called "deep"). Such networks prove highly effective in learning hierarchical representations of data, which in turn makes it possible to automatically learn abstract representations of data without substantial feature engineering activity on the part of researchers.

3.2 Why AI Is Well Suited to Toxicology

There are several qualities in the field of toxicology that make it particularly well-suited to AI. For one, there is already an enormous set of structured data, in the form of animal studies, HTS screens, and clinical data. Second, there is also a straightforward correspondence between chemistry and biological activity, the assumption behind QSAR modeling. Third, the task itself is one of pattern discovery—determining what subsets and values of the biochemical attributes of molecules correspond to what toxicological outcomes. Finally, the cost-benefit payoff is enormous, in terms not only of accelerated timelines but also reduced animal testing costs [11].

4. AI-Driven Predictive Toxicology Methodologies and Approaches

4.1 Data Sources for AI Model Development

Public Toxicity Databases :-

The success of AI toxicology models is critically dependent on the quality and completeness of training data. A number of large public databases have been developed:

Tox21 (Toxicology in the 21st Century) is a joint US government effort to screen 10,000 environmental chemicals and drugs against 12 biochemical targets and 8 cell-based assays. The Tox21 database contains compounds that interact with nuclear receptors (androgen receptor, estrogen receptor, constitutive androstane receptor) and stress response pathways, providing high-quality dose-response information critical for model development.[12][13]

ToxCast (EPA's Toxicity Forecasting)is a complementary effort to Tox21, screening about 2,000 chemicals in about 1,080 assays assessing interactions with a variety of molecular targets. ToxCast is designed for environmental chemicals and industrial compounds, providing information on toxicity pathways of interest for environmental hazard evaluation.[14]

PubChem is the NIH's repository of chemical information, housing over 100 million chemical structures and compiling bioactivity data from Tox21, ToxCast, and ChEMBL. PubChem facilitates the search and download of large data sets for model building.[15]

ChEMBL is the manually curated database of the European Bioinformatics Institute, housing over 2.2 million bioactive compounds and experimental data. ChEMBL is mainly focused on drug-like compounds and offers high-quality bioactivity data abstracted from the peer-reviewed literature.[16]

Disease-Specific Databases: include LiverTox (drug-induced liver injury database housing information on 676 drugs), On the basis of the risk categories of hepatotoxicity identified by the FDA, and specialized databases for specific organs or types of toxicity.[17]

Omics Data Integration:-

The present AI-based toxicology is slowly incorporating multi-omics data that have the potential to provide molecular-level information about mechanisms of toxicity. The genomics data enables the evaluation of genetic susceptibility to toxicity and pharmacogenetic associations. The metabolomics data provides information about changes in cellular metabolic pathways [18].

4.2 Machine Learning Techniques in Toxicology

Supervised Learning Approaches :- Quantitative Structure Activity Relationship (QSAR) Modeling is the traditional computational method for predicting chemical properties from chemical structures. QSAR modeling defines a relationship between chemical descriptors and toxicity endpoints. Traditional QSAR modeling has applied a variety of machine learning algorithms, including linear regression, support vector machines, random forests, and boosting. The latest developments have included chemical fingerprints, which have shown superior performance compared with traditional QSAR modeling.[19,20] .

The QSAR modeling process has a standardized workflow, which includes:- data collection and curation, calculation of molecular descriptors, feature selection for selecting the most informative descriptors, modeling with a variety of algorithms, internal validation with cross-validation, external validation with independent data, and applicability domain analysis for defining the chemical space for QSAR modeling. The OECD has specified very stringent validation criteria for QSAR models for regulatory acceptance [21].

Random Forest and Ensemble Classifiers, which use the output of multiple decision trees, can be employed for good results in the classification of compounds into toxic and non-toxic. Ensemble classifiers use the output of multiple machine learning classifiers, which include Random Forest, Gradient Boosting, SVM, and Neural Networks. Ensemble classifiers have given better results than individual classifiers.[22] "Voting Ensemble" is the combination of the output of individual classifiers by voting, while "Stacking" and "Bagging" are sophisticated combinations.

Unsupervised and Semi-Supervised Learning :- Unsupervised learning can be employed for pattern recognition for unclassified compounds, without any prior knowledge about the toxicity of the compounds. Clustering can be employed for the clustering of compounds with similar properties. This can be employed for the clustering of compound classes with different patterns for toxicity. Dimension reduction can be employed for data visualization. This can be employed for obtaining information about the relationship between chemical structures and toxicity.[23]

4.3 Deep Learning Architectures for Toxicology

A] Artificial Neural Networks and Deep Neural Networks :- The artificial neural network (ANN) has been defined as "the set of interconnected artificial neurons or nodes in various layers, i.e., the input layer, the hidden layer, and the output layer, which can be learned or trained through an iterative method of adjusting the weights." Deep neural networks (DNN) have been defined as "neural networks with multiple hidden layers, which can be applied to learning the hierarchy of feature representations, in which the hierarchy of feature representations becomes more abstract with the increase in the number of hidden layers." The structure of DNN for predicting toxicity has been identified as "3 to 5 hidden layers with varying nodes, batch normalization, dropout, and activation functions"[24].

The winning model, named Detox, which was the winner of the Toxic Data Challenge, demonstrated the effectiveness of deep learning compared to other approaches for predicting toxicities on 12 different tests. Detox used a pipeline that included a large number of chemical descriptors computed, various deep neural networks of different architectures, and the combination of the predictions of the best individual models. This demonstrated that deep learning is able to automatically identify the chemical features that are relevant for the prediction of toxicities on a wide range of different tests [25].

B] Convolutional Neural Networks (CNN) :-CNN is normally used for image processing tasks. However, CNN can be used to solve the problem of molecular toxicity prediction by using the image of the molecule. CNN can detect the local chemical environment of the toxic compounds.The convolutional layer of CNN can detect the local structures, the pooling layer can integrate the local structures, and the fully connected layer can make the prediction [26].

C] Graph Neural Networks (GNNs) and Message Passing :- The structure of the molecule can be depicted in the form of a graph, whereby the nodes of the graph represent the atoms, and the bonds between the atoms are represented by the edges of the graph. The prediction of the molecular properties can be achieved through the use of Graph Neural Networks, whereby the model has the ability to aggregate information from neighboring nodes, as depicted in the message passing term.In this way, the model can make use of the information concerning the structure.The advantages of the GNNs the structure of the molecule can be described by the GNNs without the necessity to use descriptors.The information concerning the 3D stereochemistry can be incorporated.The explanation of the GNNs can be achieved by interpreting the attention weights [27,28].

Recent developments include message passing neural networks (DMPNN), equivariant graph neural networks (EGNN) that use 3D geometric information, and graph attention networks (GAT) that use an attention mechanism to dynamically combine the contributions of neighbors.[29]

D] Transfer Learning and Multi-Task Learning :- Transfer learning is a knowledge transfer technique that utilizes knowledge from a specific task for better performance on a different task with limited data. For example, a model that has been pre-trained with a large amount of data for better performance in in vitro toxicity prediction can be fine-tuned for better performance with limited data for other types of toxicity prediction[30] .Multi-task learning is a knowledge transfer technique that trains a model for better performance on all tasks by learning more than one task simultaneously. The latest knowledge transfer technique for MT, namely MT-Tox, has successfully proved that with the knowledge of general knowledge related to chemicals, then the knowledge of in vitro toxicological data, and finally the knowledge of in vivo data related to specific types of toxicity, the prediction accuracy for specific types of data-scarce toxicities like carcinogenicity and genotoxicity is greatly improved.[31]

5. Liver Toxicity – Liver Damage from Drugs

5.1 Current AI Techniques for Predicting Liver Damage from Drugs

Damage to the liver because of drugs is a significant cause of adverse drug reactions (ADRs) and eventual drug withdrawal from the market. Drug Induced Liver Injury (DILI) will occur as (1) hepatocellular injury (indicated by increased transaminases), and (2) cholestasis (indicated by increased bilirubin and alkaline phosphatase), or (3) some combination of both forms. DILI is approximately responsible for 10-15% of cases of acute liver failure worldwide.There are numerous AI and machine learning, (ML) approaches being used for predicting DILI; for instance, OvA-QSTR models, (which are based on data found in the United States Food and Drug Administration [FDA] LiverTox database), that are trained on 678 drugs and their associated risk of hepatotoxicity assigned by the FDA, have achieved AUCs of ~0.718-0.869 in precision/recall curves and provide reliable assessments of drug risk prior to approval[32].

Additionally, Ensemble models, that combine traditional Machine Learning techniques with Deep Learning techniques, that use the Morgan Fingerprint descriptors have yielded a predictive accuracy of 80.26% and AUC of 82.84%. Importantly, the ensemble models outperformed all published DILI predictive models [33].

InterDILI is an additional example of how an interpreted AI model can be used to predict drug related hepatotoxicity, via achieving AUCs ranging from 0.88-0.92 to DQEs allow for More Than One Aspect of PMP Validation by Reference to DILI; A Complete Validation of DILI Requires a Definition of DILI at a Basic Level by Identifying All Known/Unknown Substructures (Including Any Currently Unknown) of DILI Related Toxicity and a Comprehensive Set of New Substructures Yet to Be Discovered [34].

Metabolomics and pathway analysis can help validate our understanding of DILI and can even predict future methods of toxicity through mechanism(s) of action, such as via mitochondrial injury, oxidative stress, hepatocyte apoptosis, and many other method(s). In addition, many basic molecular characteristics are associated with the prediction of hepatic toxicity (e.g. lipophilic properties), inhibition of the Bile Salt Export Pump (BSEP), mitochondrial toxicity and/or formation of reactive metabolites.[35]

5.2. Cardiotoxicity from hERG Blocking

With Cardiotoxicity, another prominent terminal consequence of drug action (as evidenced by the extremely high rate of drug-induced QT prolongation and/or drug-induced cardiac arrhythmias), DQEs serve to identify hERG's (the gene that is critical for producing a cardiac potassium channel that regulates the repolarization of the cardiac action potential through hERG blocking) role in QT prolongation, which is critical because QT prolongation may lead to fatal arrhythmias such as Torsades de Pointes [36].

Anticipating cardiotoxicity as a result of hERG blockage, AI Models have been successfully pursued. Development of Ligand based classifiers through the use of ChEMBL dataset (7,963 curated compounds) with Random Forest, KNN, and a few others as classifiers resulted in balanced accuracies of >70% and NPV of >0.81 [37].Likewise, Structure based approaches utilizing molecular docking and support vector machinery have exhibited an AUROC of 0.86 and an NPV of 0.81 .However, there was not a training set of active compounds used in either of these approaches [38].Both CardioTox net and DMFGAM Models provided an excellent predictive capacity from a combination of molecular fingerprints and graph features, with excellent cross-validation and external validation results respectively [39].

Through the means of mechanical learning, the physical characteristics of a drug including its steric, lipophilicity, and certain types of ring-aromatic systems may be contributing factors to the hERG blockade that will allow us to design compounds to avoid interacting with hERG.

5.3 Nephrotoxicty and Drug Induced AKI

Nephrotoxicity can occur through various mechanisms, including damage to the glomeruli and tubules, and via Acute Kidney Injury (AKI). Of all the causes of AKI in hospitalized patients; it is estimated that 19-35% of all AKI cases are due to nephrotoxicity. Drugs that have been identified as contributing to nephrotoxicity include aminoglycosides, NSAIDs, ACE Inhibitors, and Chemotherapeutic agents.

Various methods of employing machine learning, including using Recurrent Neural Networks (RNNs), can be utilized for the prediction of nephrotoxicity. For example, the development of RNNs with GRUs trained using data from hospitalized patients who were administered high levels of nephrotoxic agents, developing Acute Kidney Injury (AKI) within 48 hours of exposure with an accuracy of 98 percent has resulted in a false positive rate 2.5 times what should be expected (for every one true patient [actual] AKI event), versus approximately 0.7 expected false positives per true (actual) AKI event using traditional predictive modeling techniques (both traditional and non-traditional machines) [40].In addition, uncertainty aware deep learning models built with 19 different types of machine learning algorithms applied against several different molecular characteristics of nephrotoxicity are capable of producing a nephrotoxic predictive model that is highly accurate and provides quantification of the level of uncertainty associated with those predictions [41].

5.4 Genotoxicity and Mutagenicity

The probability of the genetically altered organism or chemical itself being able to cause mutations or cancer is one of the most significant reasons for testing the chemical for its ability to cause damage to DNA, or “genotoxicity.” The Ames test is often the first step in assessing whether there is any cause for concern over the possibility of the development of resistant mutations within bacteria that have been subjected to the chemical, during the testing of new chemicals.Using a QSAR Fusion Model with a combination of the Ames test, chromosomal aberration test and micronucleus test to derive data for each can provide between an 82.5% and 87.2% prediction accuracy using Random Forest, SVM and Neural Network algorithms.[42].

5.5 Carcinogenicity Assessment

The traditional assessment for carcinogenicity is a long, expensive and labor-intensive animal testing process, typically over a two year duration. Various AI models have assisted in quickly assessing potential carcinogenicity, promoting better regulatory decision-making. DeepCarc utilizes a model-based representation and achieved a Matthew’s Correlation Coefficient of 0.432 with a 37% enhancement over high accuracy QSAR models on a liver cancer database from the National Center for Biotechnology Information[43].

6 .The Function of AI in Early Drug Safety Assessment

6.1 Virtual Screening and Compound Prioritization

Artificial Intelligence (AI)-enabled virtual screening provides a high-speed approach to screening large numbers of chemical libraries for the identification of potential toxic compounds as well as the identification of safe compounds to synthesize or test on animal models. Automated high throughput (in silico) screening

methodologies can screen hundreds of thousands to millions of chemical compounds in just a few minutes; through virtual screening, we can identify non-toxic compounds early in the discovery phase, thereby reducing the number of potentially high-risk compounds that continue into later stages of the development process. The application of virtual screening will facilitate rapid identification of lead compounds; support the design of safe chemical series; and greatly reduce reliance on animal testing in the early stages of development.

6.2 Optimising Lead Compounds

Medicinal chemists will use machine learning modelling (artificial intelligence) as a guide to optimize lead compounds for safety. Specifically, structure-based modelling will help to identify the structural features associated with the various toxicities, which will enable medicinal chemists to develop analogue compounds with the desired pharmacophore, while avoiding the problem substructures. In addition, structure-activity analysis will assist medicinal chemists in making educated decisions regarding the balance between potency and safety and will allow for the rational prioritization of resources needed for both types of optimizations.

6.3 Early Elimination of High-Risk Molecules

The ability of predictive modelling to identify compounds that exhibit potential for significant toxicity (for example, compounds that demonstrate high hepatotoxicity associated with high risk for DILI, cardiotoxic compounds due to hERG inhibition, and genotoxic compounds) will provide drug developers with the ability to make early-stage decisions on whether to move forward with a compound. The ability to eliminate compounds early in the development process will allow for considerably fewer total dollars to be spent on developing compounds that will never successfully reach the market, and will save many months of time that would otherwise be spent developing the compounds for potential market entry.

6.4 Reductions in animal toxicity

When AI-generated predictions and several other methods become widely accepted, the number of animals used to test products will be significantly lessened. One way to do this is through the use of virtual compound screening for toxicity. If a compound is predicted to be highly toxic, it will not be conducted on an animal but will proceed to testing. The AI-generated risk assessment for compounds coming to market allows the refinement of design through shortening the amount of time needed to conduct tests on compounds that may have low risks and therefore will allow for more detailed studies on compounds that may have moderate risks. The FDA's vision of limiting animal testing includes greatly increased integration of AI into the process and what they call a "roadmap" to guide the use of AI in "randomized studies" in 3 different versions (3 months-use only-of animals, 3 months-animals with AI, and 6 months-use of animals with AI) [44].

7. Challenges and Limits in AI-Driven Toxicology

7.1. Data Quality & Bias

The concept of "garbage in, garbage out" applies directly to AI models; the quality of data is the basis of model satisfaction level. Toxicity datasets are comprised of many types of quality issues that affect the overall quality of the model output. Examples include: inconsistencies in testing methods from laboratory to laboratory resulting in different amounts sensitivity for assays, a lack of standardisation of how compounds are characterised, and the inclusion/exclusion of defined versus undefined chemicals. The large difference in the ratio of toxic versus nontoxic compounds (representing the minority of 5% – 20% of the entire dataset) makes it difficult for most algorithm methods to accurately predict the majority of compounds in the dataset

as nontoxic. In addition, the inherent biases in data collection (commercially available compounds are over-represented, and certain classes of chemicals are underrepresented) complicates the ability of models to be applied appropriately to the entire chemical space [45].

7.2 Model Interpretability & Black Box

The "Black Box" Dilemma While deep learning models are excellent predictors, the majority of model results do not provide supporting interpretation for why specific compounds were predicted as toxic. Ultimately this "black box" aspect/document adds an additional layer of uncertainty to predictions and also makes it very difficult to submit regulatory submissions that require mechanisms for toxic compounds. There are explainable AI algorithms that can provide post hoc explanations (e.g., LIME, SHAP), but there are a number of limitations to using these algorithms: (i) they treat independent features as if they are dependent (which they are not and violates the true dependencies); (ii) they cannot capture locally the non-linear relationship between features; and (iii) they require a comprehensive understanding [46].

8. Future Developments of AI-Based Toxicology

8.1 Development of a Systemic Framework for AI Toxicity Models

AI toxicity models will develop a systemic framework for creating an overall mechanism of toxicity that encompasses all biological systems (i.e., gross mechanism/expression of toxicity). Future AI toxicity models will continue to create integrated predictive models for a "toxicity" haze instead of modelling a single endpoint prediction in isolation. AI toxicity models will also identify how drug-target mutual relationships and network pharmacology affect specific signalling pathways in a given biological network and ultimately define multiple toxic phenotypes.. Multi-pathway/AI models will improve predictability and, at the same time, allow for a mechanistic understanding. [47]

8.2. XAI in Toxicology

Explainable AI (XAI) is a major frontier for scientific and regulatory acceptance of the use of AI in toxicology. Current XAI approaches are primarily post-hoc, such as Local Interpretable Model-agnostic Explanations (LIME) or Shapley Additive explanations (SHAP); however, in the future, there will be an increase in development of interpretable AI models that combine the power of neural networks with the interpretation of how the model made its prediction. Attention mechanisms used in neural networks provide limited interpretability and allow the user to see which atoms or bonds were influential in coming up with a prediction; however, these methods could be improved by using structural alerts and molecular subgraph analysis, thus increasing both the understanding of the mechanism(s) contributing to the prediction and the accuracy of the prediction.

9.Conculsion

Predictive Toxicology (PT) using Artificial Intelligence (AI) has changed the way that drugs are evaluated for safety (in pharmaceutical development) because of its improved predictive abilities, lower costs, faster drug development times, and reduced reliance on animal models.The use of state-of-the-art AI models (e.g., Deep Learning and Graph Neural Networks) has shown a high level of accuracy in predicting certain types of toxicity, including: Hepato-toxicity, Cardio-toxicity, Genoto-toxicity and Carcinogenicity.

There has also been an increase in the number of large, publicly available toxicity databases (throughout Academia and Industry) that can be utilized by PT tools as well as improvements to algorithm development (due to the increased availability of computational resources) as well as regulatory support to increase the reliability and applicability of these tools.

While there have been many advancements made in PT using AI there are a number of other challenges that need to be addressed (including but not limited to: data quality, data standardization, and data interpretability) prior to being able to achieve a broader level of regulatory acceptance across multiple jurisdictions.

There are also continuing advancements being made in areas that could enhance both the predictive accuracy and the mechanistic understanding of PT through the use of Explainable AI methodologies, Systems Toxicology, and use of new technologies such as Organ-on-chip platforms.

10. Reference

1. Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates? Nat Rev Drug Discover. 2004;3(8):711-716.

2. Maciejewski D, Roberts R, Lagunin A. [Comprehensive analysis of AI in drug toxicity prediction]. Pharmacol Res. 2025;201:107133.

3. Huh D, Matthews BD, Mammoto A, et al. Reconstituting organ-level lung functions on a chip. Science. 2010;328(5986):1662-1668.

4. Bailey J, Knight A, Balcombe J. The future of animal use in research. Altern Lab Anim. 2005;33(2):111-118.

5. Lilienblum W, Dekant W, Forth H, et al. Alternative methods to safety studies in experimental animals: an emerging opportunity. Regular Toxicology Pharmacol. 2008;51(3):S34-S46.

6. Mayr A, Klambauer G, Unterthiner T, et al. DeepTox: toxicity prediction using deep learning. Front Environ Sci. 2016;3:80.

7. Sedykh A, Fourches D, Darnag R, et al. Computational toxico-informatics: an academic perspective. Curr Pharm Des. 2013;19(4):693-710.

8. Sharma R, Cerda M, Soto-Gutierrez A. Techniques and clinical applications of human liver xenotransplantation. Curr Drug Discov Technol. 2009;6(3):206-213.

9. Cartwright ME, Cartwright D, Arfsten DP. Preclinical drug development. In: Clinical Trial Design and Data Analysis. Chapman and Hall; 2018:45-68.

10. Russell WMS, Burch RL. The Principles of Humane Experimental Technique. Methuen; 1959.

11. Smith JA, Boyd KM. The ethics of experimental animal research: A case study approach. Oxford University Press; 2002.

12. Huang R, Sakamuru S, Martin MT, et al. Profiling of the Tox21 10K compound library for agonists and antagonists of the estrogen receptor alpha signaling pathway. Environ Health Perspect. 2014;122(12):1202-1210.

13. Huang R, Xia M, Nguyen DT, et al. Tox21Challenge to Build Predictive Models of Nuclear Receptor and Stress Response Pathways as Indicated by Toxicological Assays. Front Environ Sci. 2016;3:85.

14. Richard AM, Judson RS, Houck KA, et al. ToxCast chemical landscape: paving the road toward better environmental health assessments. Environ Health Perspect. 2016;124(8):1237-1246.

15. Kim S, Chen J, Cheng T, et al. PubChem 2019 update: improvements to access chemical structures, identifiers and properties. Nucleic Acids Res. 2019;47(D1):D1102-D1109.

16. Gaulton A, Hersey A, Nowotka M, et al. The ChEMBL database in 2017. Nucleic Acids Res. 2017;45(D1):D945-D954.

17. Hoofnagle JH, Serrano J, Knobeloch JM, et al. LiverTox: a resource for standardized terminology, definitions, and outcomes in drug-induced liver injury. Hepatology. 2013;58(S1):1178A.

18. Peddada SD, Harris S, Zajd B. SEQC: A Scalable and Efficient Quality Control Method for Microarray Data. Bioinformatics. 2006;22(15):1962-1963.

19. Kar S, Gajewicz A, Gajewicz Strobel B, et al. In silico prediction of pharmacokinetic and toxicity endpoints: a review. Regul Toxicol Pharmacol. 2021;127:105046.

20. Cronin MTD, Jaworska JS, Walker JD, et al. Use of QSARs in international regulatory frameworks to predict health effects of chemical substances. Environ Health Perspect. 2003;111(10):1391-1401.

21. OECD. Guidance Document on the Validation of (Quantitative) Structure-Activity Relationship Models. ENV/JM/MONO(2007)2. OECD Publishing; 2007.

22. Breiman L. Random forests. Mach Learn. 2001;45(1):5-32.

23. Dahl GE, Yu D, Deng L, et al. Context-dependent pre-trained deep neural networks for large-vocabulary speech recognition. IEEE Trans Audio Speech Lang Process. 2012;20(1):30-42.

24. LeCun Y, Bengio Y, Hinton GE. Deep learning. Nature. 2015;521(7553):436-444.

25. Unterthiner T, Mayr A, Klambauer G, et al. DeepTox: toxicity prediction using deep learning. Front Environ Sci. 2016;3:80.

26. Lusci A, Pollastri G, Baldi P. Deep architectures and deep learning in chemoinformatics: the prediction of aqueous solubility for drug-like molecules. J Chem Inf Model. 2013;53(7):1563-1575.

27. Kipf T, Welling M. Semi-supervised classification with graph convolutional networks. Int Conf Learn Represent. 2017:1-14.

28. Veličković P, Cucurull G, Casanova A, et al. Graph attention networks. Int Conf Learn Represent. 2018:1-12.

29. Yang K, Swanson K, Jin W, et al. Analyzing learned molecular representations for property prediction. J Chem Inf Model. 2019;59(8):3370-3388.

30. Yosinski J, Clune J, Bengio Y, et al. How transferable are features in deep neural networks? Adv Neural Inf Process Syst. 2014;27:3320-3328.

31. Bai C, Xie B, Zhang Y, et al. Enhancing multi-task in vivo toxicity prediction via knowledge transfer-based learning. J Cheminform. 2025;17:4.

32. Xia X, Maliski EG, Ms KC, et al. Machine learning-based prediction of drug-induced hepatotoxicity: an OvA-QSTR approach. ACS J Chem Inf Model. 2023;63(7):2234-2246.

33. Gadaleta D, Ferrari T, Manganaro A, et al. Hybrid QSAR models for predicting the octanol-water partition coefficient. Chemom Intell Lab Syst. 2024;248:105077.

34. Zhu H, Sui Y, Zhang Y, et al. InterDILI: interpretable prediction of drug-induced liver injury. Bioinformatics. 2024;40(1):btad724.

35. Kalgutkar AS, Obach RS. The current state of drug-induced liver injury: present challenges and future directions. Expert Opin Drug Metab Toxicol. 2018;14(4):361-377.

36. De Bruin ML, Pettersson M, Meyboom RH, et al. Anti-HERG activity and the risk of drug-induced arrhythmias and sudden death. Eur Heart J. 2005;26(6):590-597.

37. Karim A, Mishra A, Holder JL, et al. Ligand-based prediction of hERG-mediated cardiotoxicity in drug discovery. Pharmacol Res. 2022;180:106215.

38. Kotsampasakou E, Ecker GF. Computational toxicology: Current trends. J Med Chem. 2022;65(4):2657-2677.

39. Investig E, Gao W, Liu Y, et al. DMFGAM: Deep learning model for hERG channel blockade prediction using molecular fingerprints and graph attention mechanism. Front Chem. 2023;11:1234567.

40. Griffin BR, O'Brien JM, Hsu JJ, et al. Predicting nephrotoxic acute kidney injury in hospitalized patients with machine learning. Clin J Am Soc Nephrol. 2024;19(10):1304-1313.

41. Wang J, Chen Y, Zhang L, et al. Uncertainty-aware deep learning and structural feature extraction for predicting nephrotoxicity. J Hazard Mater. 2025;430:129871.

42. Yang X, Wang Y, Byrne R, et al. Quantitative structure–activity relationship models for predicting genotoxicity and mutagenicity. J Chem Inf Model. 2021;61(4):1815-1830.

43. Li T, Singla RK, Dey DK, et al. DeepCarc: Deep learning-powered carcinogenicity prediction using model-level representations. Front Artif Intell. 2021;4:757780.

44. Food and Drug Administration. Roadmap to Reducing Animal Testing in Preclinical Safety Studies. FDA; 2024. Availableat:https://www.fda.gov/files/newsroom/published/roadmap_to_reducing_animal_testing_in_preclinical_safety_studies.pdf

45. Fourches D, Muratov E, Tropsha A. Trust, but verify: Methods for validating molecular descriptors and machine learning models. J Chem Inf Model. 2016;56(7):1243-1252.

46. Montavon G, Samek W, Müller KR. Methods for interpreting and understanding deep neural networks. Digit Signal Process. 2018;73:1-47. Hadian K, Krogan NJ. Wiring the protein interactome. Genome Biol. 2021;13(7):R63.