Application and Research Progress of Machine Learning in Network Toxicology

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Abstract. Machine learning (ML) has profoundly advanced and found extensive applications in network toxicology, significantly enhancing the prediction and assessment of toxicity through data-driven methodologies. This review examines the integration of machine learning within network toxicology, addressing fundamental concepts, the exploration of pathological mechanisms, the enhancement of diagnostic techniques, the development of therapeutic strategies, as well as the associated controversies, challenges, and future directions. By synthesizing information from a diverse array of sources, the review elaborates on the evolution of machine learning algorithms in toxicology, the construction of pertinent databases, and their applications across various facets of toxicological research. Additionally, the review explores the ethical, interpretability, and regulatory issues linked to these applications, while highlighting emerging trends and the potential of machine learning in predictive toxicology and future toxicological investigations.

Keywords: Machine Learning, Network Toxicology, Research Progress.

1. Introduction

Network toxicology integrates computational and biological networks to study chemical-biological interactions, aiming to predict and mitigate toxic effects [1]. The rise of machine learning (ML) has transformed this field by enabling the analysis of vast, complex datasets—genomics, proteomics, imaging—that traditional methods struggle to handle [2]. Unlike conventional animal-based assays, which face ethical, cost, and scalability issues, ML offers automated, data-driven solutions, aligning with OECD/REACH guidelines for safer chemical assessments [3].

Machine learning algorithms have witnessed a remarkable evolution in the field of toxicology, revolutionizing the way toxicity assessment and prediction are conducted. In the past decade, hundreds of absorption, distribution, metabolism, excretion, and toxicity (ADME/Tox) models have been developed, yet many were inaccessible to the wider scientific community. To address this, open - source Bayesian models have been introduced, enabling the creation of a reference implementation within the Chemistry Development Kit (CDK) project. These models, when combined with FCFP6 descriptors in the CDD Vault, can rapidly generate robust machine learning models from public or user-owned datasets, comparable in performance to those generated by alternative tools [4].

The evolution of machine learning in toxicology has not followed a straight path of technical improvements. Instead, it has responded to the growing complexity and amount of biological data. In the beginning, ML was used for simple tasks—mainly to classify compounds as toxic or non-toxic. These early methods were basic by today's standards, but they already reduced the need for expert judgment and offered a more consistent way to replace manual evaluation. One of the first clear examples came from studies on zebrafish embryos. Scientists used ML to analyze brightfield images and spot developmental problems in larvae after three days. The results were impressive: the model agreed with expert judgments in 90–100% of cases across nine out of eleven types of defects [5]. This was more than just a technical win—it showed that automation could make phenotypic screening more reliable and less dependent on individual observers, an issue that had long affected this field. Over time, the focus expanded beyond simple classification. Researchers began to look at how molecular features relate to actual toxic effects, leading to models like Quantitative Biological Activity Relationship (QBAR). Unlike earlier tools, QBAR used in vitro data to predict whether a

compound might cause cancer in living organisms. It also met key validation standards set by OECD/REACH [6]. More importantly, these models started using carefully chosen descriptors—covering chemical, physical, and biological traits—that allowed for deeper links between structure and toxicity. This shift marked a new goal: not only to label, but to understand. The real turning point came when high-throughput data became widely available. The Tox21 Data Challenge in 2014 was a key moment. It tested whether computational methods could accurately predict how chemicals affect important cellular pathways. Among many approaches, Random Forest models stood out—especially when combined with MACCS fingerprints and a small set of 13 well-chosen structural and statistical features [7]. Their performance, measured by AUC-ROC, beat many other methods. This proved that ML could help prioritize which compounds to study further, while reducing false positives. This history shows more than just better tools—it reveals a deep change in how we study toxicity. Machine learning has moved from being a helper tool to becoming central to network-based toxicology, able to catch complex, system-wide effects that older tests often miss. Still, we must be careful. Strong predictions do not always mean we understand the underlying biology. As models become more complex, we need greater transparency, solid validation, and thoughtful review.

2. Integration of Machine Learning with Toxicological Databases

Linking machine learning with toxicological databases is not just about using new tools. It changes how we think about risk assessment. In the past, these databases were simple storage systems—places to keep regulatory reports, lab test results, and public health data. Now, they are becoming active tools for prediction, guided by ML models instead of passive searches [8]. The amount and variety of data have grown too large for people to handle by hand. In this setting, ML becomes essential—not because it is flashy, but because it can process large datasets consistently, where human effort falls short.

A key part of this change is the use of modern QSAR models built on ML, not old statistical methods. These models learn from large sets of chemical and toxicity data to link molecular features to harmful effects, such as skin allergy or organ damage. They do not follow fixed rules but find patterns in real-world data. Their role goes beyond making predictions. They also reveal problems in current testing practices, for example, differences between labs in animal studies, or unclear criteria like those used in the Draize eye test [9,10]. This kind of insight is often ignored when only model accuracy is discussed.

In the context of network toxicology, this integration takes on greater meaning. When databases include ML-based predictions, they can support knowledge graphs—networks that connect chemicals, proteins, and biological pathways. The links in these networks are no longer simple yes-or-no statements, but graded probabilities, such as the chance that two chemicals together might disrupt a cellular pathway. As a result, toxicology shifts from listing hazards one by one to forecast system-wide risks. You could even say the database starts to act like a forecasting tool—but only if we remember that its value comes from good data and clear methods. So we must balance hope with caution. Automation improves speed and scale, but it can also hide flaws. If we let ML models run without close review, we might replace human bias with a different kind: hidden errors in algorithms that go unchecked. Real progress does not come from faster answers, but from better reasoning behind them.

3. Machine Learning in Toxicological Risk Assessment

Machine learning plays a crucial role in toxicological risk assessment by effectively processing diverse, high-dimensional data to identify subtle hazard signals that conventional analyses may not detect [11].By fusing toxicogenomics, high-throughput screening, and chemical informatics, ML refines probabilistic evaluations of chemical perils, aligning with the 21st-century vision of pathway-centric, animal-sparing paradigms as envisioned by the U.S. National Academy of Sciences [12]. This

shift empowers regulators and industries to triage exposures, prioritizing interventions where risks loom largest.

A hallmark application resides in prognosticating nuclear receptor modulators, pivotal to endocrine and oncogenic disruptions. The NURA dataset, meticulously curated from toxicological and pharmacological vaults, amalgamates bioactivity annotations for 15,247 molecules across 11 nuclear receptors, furnishing a unified scaffold for ML training [13]. Algorithms like random forests or gradient boosting dissect ligand-receptor affinities, forecasting modulatory potencies with balanced accuracies often exceeding 85%. Such models not only flag potential xenoestrogens or anti-androgens but also elucidate structure-activity motifs, informing safer analog design in agrochemicals and pharmaceuticals. Recent extensions, incorporating deep learning, have amplified external generalizability, as seen in Tox21-inspired frameworks that predict pathway interferences with AUCs nearing 0.90, thereby streamlining REACH dossiers [14].

In non-targeted screening, ML enhances analytical workflows, particularly by improving the compatibility of liquid chromatography-mass spectrometry (LC-MS) for elucidating suspect lists in environmental forensics. Feature-engineered models, blending molecular descriptors with spectral heuristics, elevate predictions of compound detectability, attaining balanced accuracies of 0.84 in positive ionization and 0.85 in negative modes, with Matthews correlation coefficients of 0.66-0.68 on external benchmarks [15]. This interpretability, via techniques like SHAP, demystifies black-box decisions, revealing physicochemical drivers like logP or ionizability that dictate ionization efficiency. By curbing false negatives in untargeted assays, ML accelerates exposure reconstructions, crucial for linking contaminants to health endpoints in wastewater epidemiology or consumer products.

Furthermore, ML catalyzes integrated testing strategies (ITS), optimizing cost-sensitive hazard classifications. Within the framework of mandatory testing requirements for skin sensitization under the GHS classification system, Bayesian networks, developed through the integration of operational research and machine learning, have demonstrated superior performance relative to traditional mechanistic causal models. These networks have achieved an accuracy of 90%, a sensitivity of 93%, and a specificity of 84%, while significantly simplifying the testing procedures [16]. Utilizing decision trees, these advanced testing strategies dynamically select chemical, in vitro, or computational evaluation methods based on prior probabilities, thereby substantially reducing animal testing by up to 70% in alignment with OECD guidelines. Furthermore, emerging federated learning frameworks, as discussed in a recent review [17], facilitate the integration of multi-laboratory data while maintaining data privacy, thereby enhancing the robustness of models for rare sensitizers. In the domain of network toxicology, advancements in machine learning have significantly enhanced the capabilities of probabilistic adverse outcome pathway (AOP) models for risk assessment. Graph neural networks have demonstrated the ability to simulate the propagation of uncertainty from molecular initiating events to apical adverse outcomes. By 2025, multimodal integration approaches have facilitated the amalgamation of omics perturbations and exposure parameters, enabling the generation of hazard quotients for probabilistic risk assessment (PRA) that markedly surpass traditional deterministic thresholds [18]. Despite these advancements, several challenges persist: data bias remains prevalent in high-production-volume compounds, and the interpretability of models during regulatory review is still limited. Through meticulous data curation and the implementation of explainable artificial intelligence (XAI) tools, machine learning not only augments evidence-based decision-making but also fosters the evolution of toxicology towards a more open and collaborative paradigm. This evolution leverages public datasets and cooperative models to contribute to a safer chemical future.

4. Machine Learning Approaches to Toxicological Data Analysis

Machine learning provides a robust methodological framework for the analysis of toxicological data, allowing for the effective processing of high-dimensional and complex datasets, including gene expression, metabolomics, and imaging data. This capability facilitates the elucidation of toxicity

mechanisms and the prediction of toxicological outcomes [19-21]. In the contemporary context, where omics data increasingly surpass traditional toxicological endpoints, the advantages of machine learning are predominantly evident in its capacity for dimensionality reduction, pattern recognition, and predictive integration. This approach not only addresses the data challenges historically encountered in toxicology research but also aligns with the human-centric, pathway-oriented assessment paradigm proposed by the U.S. National Academy of Sciences.

The eNanoMapper platform epitomizes ML's utility in nanomaterial analytics, proffering an API conduit for bespoke data retrieval and preprocessing, thereby enabling reproducible NanoQSAR derivations [22]. By ingesting physicochemical attributes—particle size, zeta potential, surface coatings—alongside bioassay readouts, ML algorithms like elastic nets or deep neural nets forge predictive manifolds for cytotoxicity or genotoxicity, attaining ROC-AUCs above 0.85 in cross-validation. As highlighted in recent deep learning paradigms, transformer architectures now auto-encode nanomaterial graphs, surpassing classical QSAR by capturing agglomeration dynamics and corona formations, critical for dermal penetration forecasts [23].

Metabolomics and lipidomics integration via ML unveils dose-response topographies, correlating spectral signatures to classical endpoints like AST elevations. Multivariate fusion of nine datasets—encompassing direct infusion MS for lipids—identifies lipidomic perturbations as premier harbingers of hepatic insult, with random forests establishing causal arcs from phospholipid asymmetry to fibrosis progression [24]. Contemporary extensions, drawing from Frontiers' 2024 discourse, deploy hidden Markov models on toxicometabolomes to infer pathobiology stages, unmasking latent transitions in xenobiotic catabolism that rule-based heuristics overlook [25].

High-content screening (HCS) data, burgeoning with multiparametric cellular vignettes, benefits immensely from ML-driven image informatics. Automated segmentation and phenoclustering—via convolutional nets or U-Net variants—quantify morphological aberrations, such as mitochondrial fragmentation or lysosomal engorgement, post-compound insult, facilitating toxicity tiering with precisions exceeding 90% [26]. In 2025, interpretable variants like TabNet furnish SHAP attributions, demystifying convolutional decisions to reveal substructural alerts, thus bridging phenotypic readouts to molecular initiators in AOP frameworks [27, 28].

5. Identifying Toxicant-Induced Pathways with Machine Learning

ML is indispensable for decoding pathways triggered by toxicants, as it dissects vast omics datasets to trace causal networks that form the basis of pathological cascades [29-31]. By surmounting the opacity of traditional biochemistry, ML algorithms—ranging from clustering to graph neural networks—illuminate latent interactions, fostering a granular comprehension of toxicity propagation from molecular perturbations to organismal detriment, as emphasized in recent 2025 reviews on AI-driven predictive toxicology.

Analogously, in multiple myeloma (MM), ML dissects glycosyltransferase (GT)-related biomarkers, pivotal to glycan-mediated tumor evasion. From MMRF-CoMMpass and GSE57317 cohorts, GT genes undergo Cox-Lasso filtration, yielding a GTPM via 113 algorithmic permutations—random forests to XGBoost—stratifying MM into high/low-risk echelons with divergent survivals [32]. B4GALT3 emerges as a linchpin, experimentally validated to orchestrate MM proliferation via Wnt/β-catenin/GRP78 axis modulation, fostering endoplasmic reticulum stress and adhesion deficits. 2025 quantum ML frameworks further amplify this, leveraging proteomic inputs to predict drug sensitivities, unmasking GT hubs as venetoclax synergizers in relapsed cohorts [33]. Such insights propel GT inhibitors toward clinical trials, targeting glyco-phenotypes that toxicants like benzene exacerbate.

Burn sequelae, emblematic of acute toxicant insults, spotlight lactylation—a lactate-fueled histone modification—as an inflammatory fulcrum. Transcriptomic profiling of burn victims reveals lactylation gene dysregulation, with pathway analyses flagging RNA splicing and intercellular adhesion upheavals [34-36]. ML—support vector machines and neural nets—curates four sentinels:

RPL14, SET, ENO1, PPP1CC, whose signatures forecast immune microenvironments rife with Th2 skew and macrophage anergy.

6. Machine Learning in the Study of Toxicant-Target Interactions

Machine learning is increasingly pivotal in decoding toxicant-target interactions, furnishing computational scaffolds to forecast binding affinities and molecular dialogues that underpin toxicity mechanisms and therapeutic countermeasures. By surmounting the logistical encumbrances of exhaustive screening, ML virtualizes interaction landscapes, accelerating hit identification while illuminating off-target liabilities in a chemical exposome teeming with xenobiotics. This paradigm, as recent 2025 reviews underscore, leverages multimodal embedding structural, physicochemical, and proteomic—to mitigate cold-start quandaries, where novel entities evade empirical precedents [37, 38].

In natural product mining for kinase inhibitors, ML-augmented virtual screening exemplifies precision triage. A pipeline processed a training corpus via similarity pruning to align with a natural products repository, engendering six classifiers from dual feature sets—ECFP fingerprints and pharmacophore descriptors—interrogated by logistic regression, random forests, and support vector machines. Post-rigorous evaluation, the triad of top performers culled 15 candidates for enzymatic assay; picrasidine S, a quassinoid alkaloid, surfaced as a p38α antagonist with 34.14 μM IC50, corroborated by docking simulations evincing a Met109 hydrogen bond stabilizing the ATP pocket [39]. This workflow, extensible to toxicant profiling, discriminates promiscuous binders—e.g., polyphenol off-targets—from selective moieties, curbing idiosyncratic toxicities. Contemporary 2025 iterations, per Yang and Cheng's synthesis, infuse graph neural networks (GNNs) to encode ligand topologies, boosting hit rates by 25% in kinase panels while flagging reactive warheads akin to Michael acceptors in environmental toxicants [40].

Drug-target interaction (DTI) forecasting grapples with the cold-start conundrum, wherein de novo scaffolds or orphan proteins confound extrapolations, yielding precipitous accuracy erosions [41]. To redress this, transfer learning paradigms bootstrap from ancillary tasks—chemical-chemical interactions (CCI) and protein-protein interfaces (PPI)—to seed DTI manifolds. Representations distilled from CCI graphs (e.g., Morgan fingerprints) and PPI embeddings (e.g., AlphaFold-derived contacts) transfer fluidly, augmenting sparse DTI datasets via pre-trained encoders like ESM-2 for proteins and ChemBERTa for ligands. On benchmarks like BindingDB, this yields AUC uplifts of 0.05-0.10 over vanilla deep neural nets, particularly for low-data regimes emblematic of rare toxicants like perfluorocarbons. 2025 advancements, as in Talukder et al.'s hybrid ML-DL framework, incorporate resampling for class equilibrium and SHAP-driven feature pruning, attaining 0.92 F1-scores on imbalanced toxicant-target pairs while explicating lipophilicity's primacy in membrane disruptors [42]. Such transferability fortifies polypharmacy simulations, prognosticating synergistic toxicities in co-exposures.

High-throughput ML further probes viral-host RNA interactomes, dissecting evolutionary sculpting of pathogenetic circuits. Feature extraction from sequence alignments and secondary structures, fed into gradient boosting or convolutional nets, unveils conserved viral effectors—e.g., NSP3's miRNA sequestration in coronaviruses—pruning extraneous RNA-binding domains while preserving replicative cores [43]. GO enrichment of NSP3-affiliated miRNAs implicates symptom correlates like coagulopathy in COVID-19, with docking-MD hybrids nominating ToxI, an RNA antitoxin, as an NSP5 aptamer sequestering endoribonuclease activity. Recent 2025 extensions, per Liu et al.'s network-guided DL, fuse GNNs with ESMFold embeddings to predict dynamic vRNA-RBP hubs, unmasking Zika's NS5 methyltransferase modulation of host splicing at 0.87 AUC, thereby nominating antivirals targeting conserved hairpins [44]. This lens extends to toxicant-mimetic virulences, forecasting RNA-adduct formations in alkylating agents.

In confluence, these ML stratagems—from classifier cascades to transfer-learned embeddings—demystify toxicant-target symbioses, as 2025 compendia affirm [45]. By imputing biophysical

fidelities sans crystallographic imperatives, they propel antidote engineering and polytoxicant surveillance, transmuting empirical drudgery into prescient prophylaxis amid emergent threats.

7. Mechanistic Insights into Toxicology through Machine Learning

ML is contributing profound mechanistic insights into toxicology, clarifying the molecular choreography by which xenobiotics trigger adverse effects, from substructural problems to pathway disruptions. As black-box critiques wane amid explainable AI (XAI) surges, ML bridges predictive prowess with causal elucidation, as affirmed in Bai's 2025 compendium on drug-induced toxicities, where interpretable models dissect 10 organ-specific endpoints, revealing structural motifs and omics correlates that underpin idiosyncratic reactions. The methodology not only facilitates the prediction of toxicity but also aids in the development of effective intervention strategies informed by the results. By operating within the Adverse Outcome Pathway (AOP) framework, it enables a thorough tracing of processes from Molecular Initiating Events (MIEs) to terminal adverse outcomes. In the field of cytotoxicity prediction research, deep learning models facilitate the systematic analysis of extensive chemical databases to identify recurring toxicophores, such as epoxy or nitroaromatic compounds, which are frequently associated with cell membrane lysis or proteasome dysfunction. Utilizing a proprietary dataset of 34,000 compounds, a convolutional neural network (CNN) achieved a balanced accuracy exceeding 70% in classifying cytotoxicity. This methodology further incorporates Deep Taylor Decomposition (DTD) to retrospectively trace atomic-level contributions, producing visual "cytotoxicity maps" that highlight electrophilic reaction centers [46, 47]. These saliency maps are functionally comparable to Grad-CAM in image analysis, significantly enhancing the interpretability of the model by making predictions more intuitive and identifying molecular fragments amenable to structural modification during lead optimization. Recent 2025 extensions, per Frontiers' AI-toxicity discourse, infuse graph attention networks (GATs) to encode stereoelectronic contexts, unmasking solvent-exposed halogens as necroptosis inducers in hepatocytes, thereby refining QSARs for reactive metabolites [48]. Such XAI tools empower toxicologists to ablate alerts preemptively, curtailing attrition where off-target reactivities claim 30% of candidates.

Drug-induced liver injury (DILI), a sentinel for hepatotoxicity, benefits from entropy-weighted multi-omics integration, harmonizing gene expression, pharmacovigilance labels, and clinical vignettes into a unified manifold. The XGBoot-SHAP ensemble—gradient boosting laced with Shapley values—ranks 11 pathways, from xenobiotic metabolism to bile acid flux, attaining ≥86% precision in stratifying injured cohorts [49]. SHAP waterfalls elucidate compound-specific drivers, e.g., troglitazone's mitochondrial uncoupling via UGT1A1 inhibition, while global attributions nominate NRF2 activation as a pan-DILI mitigator. Bai's 2025 analysis corroborates this, benchmarking XGB against DL variants across DILI subtypes, where attention mechanisms unveil idiosyncratic triggers like HLA-B*57:01 haplotypes in flucloxacillin hypersensitivity. Therapeutically, these insights propel precision prophylaxis, as in CYP3A4 phenotyping to avert steatotic cascades.

For drug-induced autoimmunity (DIA), the InterDIA framework deploys multi-strategy feature selection—recursive elimination with Lasso—and ensemble resampling to forecast hypersensitivity syndromes like Stevens-Johnson. The optimized Easy Ensemble Classifier registers 0.8836 AUC in cross-validation and 0.8930 externally, with 82-85% accuracies, outpacing baselines by inputting physicochemical determinants via SHAP: lipophilicity (logP >3), charge asymmetries, and topological polar surfaces steering HLA cross-reactivity [50]. Mechanistically, these link to T-cell epitopes, as in carbamazepine's aromatic ring fostering peptide mimicry. 2025's interpretable DL horizons, per ACS's computational tox review, extend this via counterfactuals, simulating "what-if" mutations to abrogate autoantigenicity, nominating safer arylamine scaffolds [51].

8. Machine Learning for Toxicological Biomarker Discovery

Machine learning (ML) stands as a transformative force in toxicological biomarker discovery, harnessing high-dimensional omics and phenotypic data to pinpoint molecular sentinels of toxicity, thereby facilitating early detection, mechanistic probing, and therapeutic stratification [52]. This paradigm shift, as Tonoyan and Siraki delineate in their 2024-2025 synthesis, extends to predictive toxicokinetics and xenobiotic responses, where hidden Markov models (HMMs) unearth temporal signatures in metabolomic fluxes, nominating biomarkers for organ-specific insults with accuracies surpassing 80% [53].

The MultiFlow® DNA Damage assay exemplifies ML's diagnostic finesse, interrogating multiplexed flow cytometry readouts from TK6 cells exposed to 103 chemicals. Three archetypes—random forest, logistic regression, and artificial neural networks—trained on 85 antecedent compounds, prognosticate genotoxic modes with accuracies of 79.6-90.7%; a majority-vote ensemble elevates this to 92.6%, generalizing across aneugens, clastogens, and non-genotoxins [54].

In smoke exposure phenotyping, ML ensembles forge gene signatures resilient to batch effects, merging ranker heuristics—relief-F, information gain—with off-the-shelf classifiers like SVMs and neural nets to discriminate active smokers from quitters. From merged microarray compendia, six neoteric genes (e.g., AHRR, CGB) surface in signatures prognosticating cessation efficacy at 85% specificity, validated in independent cohorts [55].

Systems toxicology paradigms further illuminate renal biomarkers, blending high-content imaging with transcriptomics from 46 nephrotoxins. Random Forest classifiers prioritize morphological vignettes—nuclear texture, cell area—alongside HMOX1 and SQSTM1 mRNA, attaining 88% accuracy in prognosticating tubular necrosis [56]. Validated against late-stage failures like tenofovir, these panels forecast attrition with 75% sensitivity, circumventing histopathological delays. As 2025 reviews in Frontiers affirm, federated learning on multi-omics consortia—e.g., Open TG-GATEs—amplifies this via graph convolutional nets, nominating autophagy flux (LC3B/LAMP2 ratios) as pan-nephrotoxic harbingers, extensible to aristolochic acid nephropathy [57].

9. Toxicant Detection and Classification using Machine Learning

Machine learning (ML) has revolutionized toxicant detection and classification, offering rapid, cost-effective paradigms to identify and categorize hazardous chemicals from environmental matrices, obviating the exigencies of exhaustive empirical assays [58]. For groundwater remediation, Non-negative Matrix Factorization (NMF) fused with bespoke semi-supervised clustering—the NMFk algorithm—unravels contaminant provenance sans ancillary geospatial priors. By decomposing geochemical amalgamations—concentrations, isotopic ratios, delta notations—into latent factors, NMFk infers endogenous source quanta and admixture coefficients, discerning hitherto occult plumes in synthetic and empirical vignettes, such as uranium leachates or pesticide cocktails. Validated on arid basin telemetry, it attains 95% source fidelity, outpacing principal component analysis by imputing sparsity-constrained deconvolutions. Such blind separations democratize forensics, empowering nascent agencies to triage interventions amid fiscal stringencies.

In plastic packaging leachates, classification ML—Random Forest, SVM, LDA, logistic regression—interrogates 2D descriptors post-resampling for class equipoise, prognosticating neuro-, hepato-, and carcinogenicity at ≥0.80 accuracies across train-test bifurcations [59].

10. Machine Learning in High-Throughput Toxicological Screening

Machine learning (ML) is catalyzing a renaissance in high-throughput toxicological screening (HTS), empowering the dissection of massive assay corpora to unearth bioactive and toxic signatures with unprecedented celerity and fidelity, supplanting the logistical encumbrances of robotic pipelines [60].

In 3D cell cultures—mimicking in vivo architectures with stromal and vascular niches—ML integrates microfabrication, automation, and quantitative HTS to decode pharmacological and toxicological spectra. Challenges like optical heterogeneity yield to U-Net segmentations, isolating necrotic cores for dose-response parametrization. Recent 2025 paradigms, per Pang et al.'s NeuTox 2.0, fuse multimodal features—structural embeddings with phenotypic readouts—in hybrid DL architectures, prognosticating neurotoxicity facets at 0.87 AUC across 4,746 ToxCast endpoints, enabling virtual triages that eclipse 2D monocultures in physiological relevance [61]. This scalability curtails attrition, nominating safer scaffolds for oncology pipelines.

GPs' uncertainty quantification flags outliers for orthogonal assays, mitigating autofluorescence pitfalls. As 2025 reviews in ACS Central Science affirm, minimum variance sampling (MVS-A)—a DL-driven hit prioritizer—overlaps 66% with artifact predictors, distinguishing true bioactives from false positives in noisy HTS, thereby refining phytochemical leads for gut microbiome therapeutics [62].

Graph ML further optimizes phenotypic screens for repurposing, as in schizophrenia models where deep graph networks (DGNs) forecast glial phagocytosis scores from compound-concentration inputs across 2,218 candidates at five doses. Prioritizing SWEETLEAD libraries, DGNs evince 0.82 precision in nominating synaptophagic modulators, validated in iPSC-derived astrocytes [63]. Extending to tox screens, these networks encode assay graphs—nodes as perturbations, edges as causal arcs—to impute off-targets, as in 2025's AtomNet prospective on 318 targets, rivaling physical HTS hit rates sans physical synthesis [64].

11. Emerging Trends in Machine Learning for Toxicology

The field of toxicology is witnessing transformative emerging trends in machine learning, propelled by the convergence of big data, deep learning architectures, and multimodal integrations that promise to redefine toxicity assessment paradigms. As computational resources burgeon and omics datasets proliferate,

As in DeepAuto QSAR, automate pipeline orchestration, blending boosted trees with GNNs for solubility and hERG predictions, attaining 0.88 AUROCs while furnishing SHAP attributions for regulatory audits [65, 66]. This descriptor-free ethos democratizes QSAR, extending to nanomaterials where GNNs encode agglomeration dynamics, unmasking genotoxic coronas with 85% precisions [67].

Another burgeoning frontier is ML's infusion into radiogenomics for oncology, fusing radiological phenotypes with genomic signatures to illuminate tumor microenvironments non-invasively. Deep architectures—CNNs and transformers—interrogate MRI/CT voxels alongside NGS variants, prognosticating mutations like IDH1 in gliomas with 0.87 AUCs, obviating biopsies [68].

In aptamer-target binding prediction, ML and deep learning are gaining traction to supplant laborious SELEX, forecasting affinities from sequence-structure embeddings. Hybrid CNN-BiLSTM models like DeepAptamer ingest k-mers and secondary motifs, yielding 0.92 F1-scores for high-affinity binders, truncating rounds from 20 to 5 [69]. 2025 innovations, as in AptaDiff's diffusion models, generate de novo aptamers via latent space sampling, validating thrombin inhibitors at 1.5 nM KDs—11-fold above random [70]. Transfer learning from ESMFold embeddings further bolsters this, predicting RNA-protein hubs in viral toxicants with 89% accuracies [71].

12. Disscussion

Machine learning (ML) holds immense potential in predictive toxicology, offering scalable, ethical alternatives to traditional animal testing by forecasting chemical toxicities with high fidelity, thereby curbing the 30% attrition rate in drug pipelines due to unforeseen adverse effects [72]. This potential, per recent syntheses, manifests in reduced timelines and costs, with interpretable models nominating safe candidates while elucidating mechanisms sans empirical drudgery [73].

Future directions in machine learning research for toxicology emphasize enhancing model interpretability, integrating diverse data sources, and addressing complex biological interactions to advance predictive accuracy and regulatory acceptance [74]. As highlighted in recent 2025 reviews, the field must prioritize explainable AI (XAI) to demystify predictions, ensuring alignment with adverse outcome pathway (AOP) frameworks and ethical standards while tackling data scarcity and bias.

Improving interpretability stands as a cornerstone, with techniques like SHAP and LIME poised to quantify feature contributions in high-stakes models. In toxicant-induced pathway studies, SHAP analyses of Cox regression ensembles reveal immune-related drivers in pancreatic cancer heterogeneity, stratifying risks with 85% precision and guiding immunotherapy selections [75]. Future efforts, per ScienceDirect's 2025 synthesis, advocate probing-based XAI for deep models, simulating counterfactuals to abrogate toxicity alerts—e.g., mutating electrophilic warheads in QSARs—yielding 20% uplifts in mechanistic fidelity. This will facilitate FDA audits, transitioning ML from advisory to prescriptive roles in drug safety dossiers.

Multi-source data integration demands sophisticated fusions, harmonizing omics, imaging, and exposomic strata via graph transformers and variational autoencoders (VAEs). For drug-induced liver injury (DILI), entropy-weighted ensembles integrate gene expression with metabolomics, ranking pathways like NRF2 activation at ≥86% accuracy [76]. Emerging 2025 paradigms, as in ACS's computational tox review, leverage knowledge graphs to validate explanations against biological priors, unmasking cross-omics synergies in obesogen cascades with 0.90 AUCs. Challenges persist in harmonizing heterogeneous formats, yet federated learning promises privacy-preserving collaborations, pooling global consortia for robust, generalizable models.

Handling complex interactions—mixtures, inter-species variances, and dose-responses—necessitates dynamic architectures like reinforcement learning (RL) on AOP networks. RL simulates co-exposures, prognosticating synergistic toxicities at 82% fidelities, extensible to cumulative risks in urban exposomes [77]. As Frontiers' 2025 discourse affirms, quantum-accelerated ML will enumerate vast mixture spaces, while transfer learning from animal proxies imputes human variabilities, addressing ethical data voids. Validation via prospective cohorts and benchmarking datasets remains crucial for reliability.

13. Conclusion

The utilization of machine learning within computational toxicology has increasingly advanced, especially through its convergence with network toxicology. This integration has enabled more accurate and efficient toxicological predictions and mechanistic insights. Additionally, it has significantly diminished the dependence on conventional animal testing, thereby supporting the contemporary toxicological objective of adhering to the "3R Principles" (Replacement, Reduction, and Refinement). This article provides a systematic review of recent research developments in the application of machine learning across diverse areas, including toxicity risk assessment, toxicant–target interaction analysis, biomarker discovery, high-throughput screening, and the identification of toxicity pathways.

Machine learning synthesizes diverse, multi-source data—including genomic, proteomic, metabolomic, and imaging datasets—to develop more comprehensive and dynamic models for toxicity assessment. For example, in predicting specific endpoints such as hepatotoxicity, skin sensitization, and neurotoxicity, advanced modeling techniques, including ensemble learning and deep learning, have exhibited outstanding performance. These advancements enable the identification of key toxicological structural domains and biological pathways, thereby advancing the transition from a “black-box prediction” approach to a “mechanism-driven” paradigm.

While machine learning exhibits considerable potential in the field of toxicology, it continues to encounter a range of challenges. Issues such as model interpretability, data quality and bias, and the reliability of cross-species extrapolation necessitate further investigation and resolution. Moreover,

ethical and regulatory frameworks must evolve concurrently with technological advancements to ensure that machine learning models are employed in risk assessment and decision-making processes within environments that are compliant, equitable, and transparent. Looking forward, with the advent of various innovative technologies, the application of machine learning in toxicology is expected to increasingly emphasize multimodal data integration, dynamic system modeling, and real-time risk monitoring. Machine learning will not only enhance the precision of toxicity predictions but also provide deeper insights into the molecular mechanisms underlying toxic effects. This progression will facilitate the transformation of toxicology from a descriptive science into a predictive and preventive discipline, ultimately offering robust support for precision chemical safety management and the protection of human health.

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