

Metabolism-Aware and Pharmacogenetics-Informed Toxicity Prediction: A Multi-Endpoint Machine Learning Framework With Systematic Platform Benchmarking

Submitted by: Sharhabil Mohamedali (igsr.sharhabil@alexu.edu.eg)

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Title: Metabolism-Aware and Pharmacogenetics-Informed Toxicity Prediction: A Multi-Endpoint Machine Learning Framework With Systematic Platform Benchmarking

Abstract:

Computational toxicity platforms typically predict safety from parent compound structure alone, ignoring metabolism-dependent toxicity and inter-individual genetic variability in drug metabolism, which together account for a substantial fraction of adverse drug reactions. Whether integrating metabolism-aware screening and pharmacogenetic simulation into multi-endpoint prediction improves safety assessment over existing platforms remains systematically unevaluated.
 We developed an open-source platform integrating six toxicity endpoints (cardiotoxicity, hepatotoxicity, mutagenicity, nephrotoxicity, cytotoxicity, and skin sensitization) with rule-based metabolite generation, cytochrome P450 (CYP) phenotype simulation across four metabolizer categories, and a novel Phenotype Sensitivity Index (PSI) quantifying how predicted toxicity varies across genetic subpopulations. We benchmarked it against two leading platforms using 284 multi-endpoint compounds with statistically calibrated decision thresholds, 30 drugs (20 withdrawn for toxicity, 10 controls), and 35 pharmacogenomic drug pairs.
 The platform achieved strong discrimination across endpoints (area under curve 0.89–0.99). For drugs withdrawn for liver toxicity, it detected 8 of 10 versus 7 of 10 for the comparator. Threshold calibration was critical: optimizing the hepatotoxicity cutoff improved specificity from 6% to 92%. Metabolism-aware screening generated 15–37 metabolites per compound and flagged reactive intermediates for known bioactivated toxicants, mechanistic information absent from parent-only tools. The PSI metric produced continuous sensitivity estimates that correctly identified drugs with established CYP-dependent metabolism while scoring non-CYP controls at zero.
 Metabolism-aware, pharmacogenetics-informed prediction adds clinically relevant dimensions missing from current platforms. The PSI metric bridges structure-based modeling and pharmacogenomics, and the open-source implementation offers a reproducible protocol for next-generation, precision risk assessment integrating artificial intelligence and new approach methodologies.

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Best Student Presentation Awards: I wish to compete

Advisor Name: Prof. Dr. Mokhtar Ibrahim Yousef

Advisor Email: yousefmokhtar@alexu.edu.eg

Degree Program: Masters

Student Meeting Attendance Grant: Yes, I wish to apply

Advisor Name: Prof. Dr. Mokhtar Ibrahim Yousef

Advisor Email: yousefmokhtar@alexu.edu.eg

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Motivation Statement:

I am a graduate researcher in biotechnology at the Institute of Graduate Studies and Research, Alexandria University, working at the intersection of computational toxicology, machine learning, and pharmacogenomics. Attending the SETAC North America 47th Annual Meeting would be a pivotal opportunity in my early research career. My work develops an open-source platform that integrates metabolism-aware screening, multi-endpoint toxicity prediction, and pharmacogenetic simulation into a single framework for next-generation risk assessment — directly aligned with the meeting's focus on integrating artificial intelligence and new approach methodologies.

Presenting at SETAC would let me share a novel contribution, the Phenotype Sensitivity Index, with the leading community in environmental and human risk assessment, and receive critical feedback from researchers advancing computational and mechanistic toxicology. Equally important, the meeting would expose me to current developments in adverse outcome pathways, in vitro to in vivo extrapolation, and weight-of-evidence frameworks that will shape the next phase of my research.

My engagement would extend beyond presenting. I intend to participate actively in session discussions, connect with researchers working on computational and pharmacogenomic approaches, and explore collaborations that could strengthen and validate my platform against external datasets. As an early-career researcher from an underrepresented region in this field, I am committed to contributing diverse perspectives and to bringing the knowledge and connections gained back to my home institution to support open, reproducible toxicology research.

Track: 1. Environmental (Human and Ecological) Toxicology and Stress Response

Session Preference: Advancing Molecular Tools and NAMs for Next-Generation (Eco)Toxicology and Risk Assessment

Presenter Name: Sharhabil Amgad Eltahir Mohamedali

Presenter Email: igsr.sharhabil@alexu.edu.eg

Author: Sharhabil Mohamedali ; Alexandria University, Egypt

Meeting Policies Agreement: I agree to abide by the SETAC meeting policies.