An Explainable 3D Graph-Transformer Framework for Hepatotoxicity Prediction with Scaffold-Aware Evaluation

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Abstract:
Drug-induced hepatotoxicity continues to be a major factor in post-market removal and late-stage drug attrition. While graph neural networks have shown promise in predicting chemical toxicity, many existing approaches rely on random data splits and offer limited interpretability, thereby reducing their reliability in real-world screening scenarios. This study presents an explainable 3D graph-Transformer framework for hepatotoxicity prediction that integrates geometric inductive bias, rigorous scaffold-based evaluation, and multiple complementary explainability approaches. Molecular structures are encoded, and spatial linkages are captured using a 3D-equivariant graph neural network. Next, a graph-level Transformer is used to model long-range atomic interactions. Five-fold scaffold cross-validation is used to assess the model on a curated hepatotoxicity dataset of 8,538 molecules obtained from Tox21 liver-related assays. We use three different explainability techniques to guarantee transparency: atom-level perturbation analysis, integrated gradients, and transformer attention visualization. Experimental results show that the proposed framework achieves 91.8% accuracy with perfect recall on the evaluated splits, while generating explanations that are chemically significant and consistent with recognized hepatotoxic substructures. The suggested method is appropriate for early-stage toxicity screening and decision support because it combines multi-view explainability with robust out-of-distribution evaluation.

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