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TDEP: Target-perturbed Differential Expression Profiles for Interpretable Drug–Target Interaction Prediction

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Accurate drug–target interaction (DTI) prediction is fundamental to drug discovery, but current computational approaches face a critical trade-off between prediction accuracy and biological interpretability. Structure-based approaches that leverage protein sequences and ligand structures offer high accuracy but often lack functional context, whereas omics-based methods using genetically or chemically perturbed expression profiles provide biological insights but suffer from noise due to off-target effects. Here, we present TDEP (Target-perturbed Differential Expression Profile), a framework that predicts target-perturbed expression profiles directly from protein sequences using drug-induced transcriptomic data. By integrating protein language models with graph learning, TDEP achieves performance comparable to state-of-the-art methods while providing explicit interpretability across 10,086 genes. To account for cellular heterogeneity, TDEP is trained separately on six representative cell lines. Predictions for unseen cell types are combined using basal-expression similarity, preserving performance comparable to within-cell evaluations. Beyond predictive performance, TDEP demonstrates biological relevance: targets with similar TDEP profiles exhibit network proximity, hierarchical clustering of TDEP reveals distinct pathway signatures, and validation against shRNA knockdown experiments shows significant enrichment (EF ≥ 2.5) among the most influenced genes. Collectively, TDEP provides an interpretable and accurate framework for DTI prediction and may help advance mechanistic understanding of drug action.