Improving QSAR Modeling for Predictive Toxicology using Publicly Aggregated Semantic Graph Data and Graph Neural Networks

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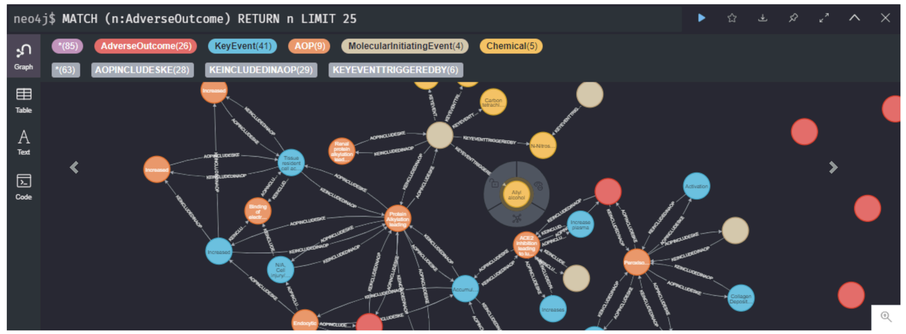
Source code: https://github.com/EpistasisLab/qsar-gnn
ComptoxAI: https://comptox.ai

Paper: https://doi.org/10.1142/9789811250477_0018

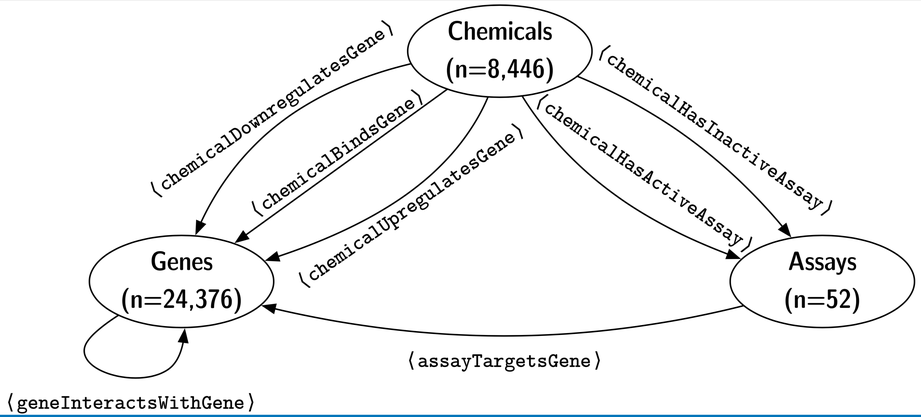
- Quantitative Structure-Activity Relationship (QSAR) modeling is the most prevalent method for *in silico* toxicity prediction.
- The disappointing performance and low interpretability of existing QSAR models call for new methodological innovation in the field.
- We introduce a GNN-based approach that aggregate data from ComptoxAI, and evaluate it on data from 52 Tox21 toxicity assays to show that it significantly outperforms existing methods.

ComptoxAI is a new graph database containing diverse entity and relationship types that pertain to translational mechanisms of toxicity

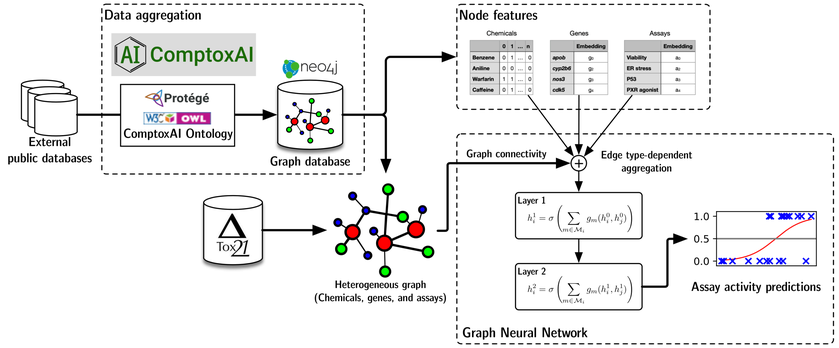


- Example view of ComptoxAI graph database

Subgraph scheme for assay outcome prediction

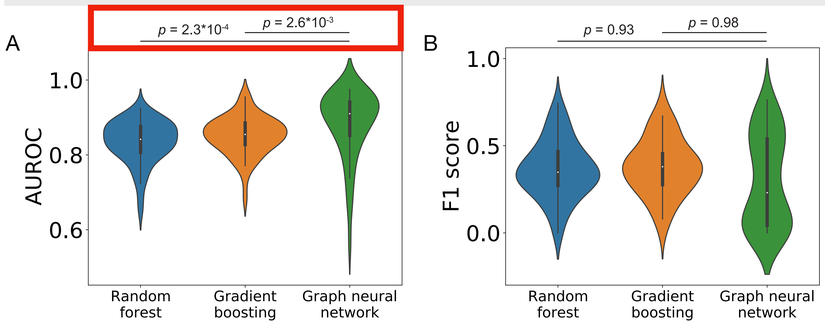


Overview of the graph machine learning approach



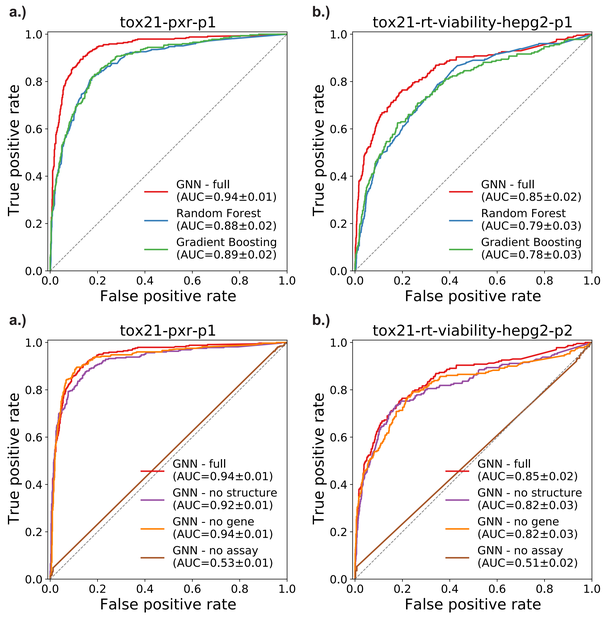
- Graph convolutional network architecture
  - Node representation
    - Chemical nodes: 166 bits MACCS fingerprint
    - Assay and gene nodes: single-valued feature optimized during model training
  - GCN layer
    - 2 hidden layers connected by leaky ReLU, softmax applied to output of the 2nd
    - Each layer is defined as an edge-wise aggregation of adjacent nodes
  - Optimization: minimizing binary cross-entropy loss with Adam optimizer

GNN model significantly outperforms baseline QSAR models



- Dataset
  - 52 assays and their accompanying chemical screening data from Tox21
  - 80%/20% train/test split on the label chemicals

GNN achieves better performance with the added context of network relationships between chemicals, assays, and genes



- **Our GNN models are highly interpretable**
  - Highest weighted assay for HepG2 viability prediction: Caspase 3/7 and Shh antagonist (both induce apoptosis)
- **Our GNN approach is robust to sources of bias**
  - The graph incorporate biological knowledge that can fill in gaps left by incomplete or inaccurate data

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