

h-MINT: Modeling Pocket-Ligand Binding with Hierarchical Molecular Interaction Network

Background/Objective

Precise modeling of protein-ligand interactions is pivotal for fundamental tasks, including the engineering of enzymes that can efficiently convert biomass-derived substrates into products. However, a central challenge for achieving accurate molecular representations lies in capturing the chemical environment of molecular fragments, as key interactions, such as H-bond and π stacking, occur only under specific local conditions. This work introduces OverlapBPE and h-MINT, an efficient tokenization-plus-learning framework for protein-ligand interactions that achieves superior performance on affinity prediction and virtual screening.

Approach

Unlike existing approaches, OverlapBPE allows overlapping fragments, reflecting the inherently fuzzy boundaries of small-molecule substructures. Together with enriched chemical information at the token level, it thereby preserves a more complete chemical context. The researchers developed h-MINT, a hierarchical molecular interaction network capable of jointly modeling interactions at both atom and fragment levels. By supporting fragment overlaps, the model naturally accommodates the many-to-many atom-fragment mappings introduced by the OverlapBPE scheme.

Results

Extensive evaluation against state-of-the-art methods shows that the model improves binding affinity prediction by 2-4% Pearson/Spearman correlation on PDBBind and LBA, enhances virtual screening by 1-3% in key metrics on DUD-E and LIT-PCBA, and achieves the best overall high-throughput screening performance on PubChem assays. Further analysis demonstrates that the method effectively captures interactive information while maintaining good generalization.

Significance/Impacts

The study demonstrates that explicitly modeling fragment overlaps is not only feasible, but necessary for preserving chemically meaningful context, leading to consistent performance gains across diverse tasks.

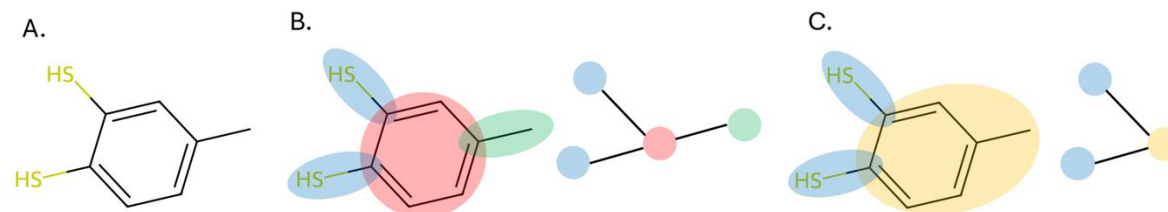


Illustration of the OverlapBPE tokenization process, depicting the A) starting molecule, B) initial fragments and token graph, and C) new fragments and token graph based on the highest-frequency composite token

Qu et al. 2026. "h-MINT: Modeling Pocket-Ligand Binding with Hierarchical Molecular Interaction Network." *International Conference on Learning Representations* 2026. DOI: 10.48550/arXiv.2604.23134.