Beating the Odds in Drug Discovery With 3DICE: Interpretable 3D Cross-Modal Learning for Drug–Target Interaction Prediction at Scale

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Drug–target interaction (DTI) prediction is a crucial step in modern drug discovery. Accurate and efficient predictions can substantially reduce costs and development time. While deep learning has advanced this field, existing methods face issues pertaining to efficient learning of drug and target feature representations, which is detrimental to generalisability and performance in cold-start scenarios. Most approaches extract representations from SMILES strings for drugs and FASTA sequences for target proteins, which encode limited 3D structural information. Additionally, many models lack explainability, being black boxes that provide little physical insight into mechanisms underlying such interactions. To address these limitations, we propose 3DICE, a novel framework leveraging co-attention-based fusion and massively pre-trained 3D structural encoders for both drugs and proteins. Uni-Mol and ESM-IF1 are employed to generate high-fidelity, 3D structure-aware embeddings which enable richer geometric and chemical understanding. Cross-modal fusion modules further augment representations to model intermolecular binding relationships. Importantly, this mechanism also provides intrinsic interpretability, highlighting and enabling qualitative analysis of most influential atoms or residues. Experiments conducted on two canonical benchmark datasets and case studies display the competitiveness of our model in real-world scenarios. 3DICE outperformed state-of-the-art models across multiple metrics on the DrugBank and KIBA datasets. Additional experiments provide a more rigorous analysis of interpretability than is typically reported in prior DTI studies, and we find that attention consistently highlights decision-critical regions which is not intrinsically class-specific.

Awards Won:
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