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BayesPPII: Interpretable and Reliable Inhibitor Prediction with Cross-Attention and Bayesian Neural Network

Dongok Nam[1], and Hojung Nam[1,*]

[1]*Department of Electrical Engineering and Computer Science, Gwangju Institute of Science and Technology*

**Corresponding author: hjnam@gist.ac.kr*

Protein-protein interactions (PPIs) are fundamental to the regulation of protein function and cellular processes, yet the development of small molecule inhibitors targeting PPIs remain challenging due to the inherent complexity of protein-protein interfaces. To address this, we present BayesPPII, an interpretable Bayesian deep learning model utilizing a cross attention mechanism to accurately predict PPI inhibitors. BayesPPII leverages diverse data representations, including pre-trained embeddings of protein sequences and molecular structures and key physicochemical properties, enriching the molecular representation. The cross-attention mechanism captures meaningful intermolecular relationships while offering interpretable insights into critical interaction hotspots between protein interfaces and small molecules. Furthermore, a Bayesian neural network with Monte Carlo dropout further calibrates prediction uncertainty, providing more robust and reliable prediction. Comprehensive validation against established benchmarks demonstrates its superior predictive performance compared to existing methods. Its interpretability elucidates critical molecular recognition patterns, accelerating rational design of PPI inhibitors. With the integration of a Bayesian neural network, BayesPPII provides reliable and well-calibrated predictions with the potential to substantially enhance hit rates in virtual screening. This work marks a pivotal advancement in computational drug discovery, facilitating the efficient identification of novel therapeutic candidates targeting PPIs.