[BIOINFO 2024]

Development of multi-task learning classification model for predicting CYP450 enzyme inhibition

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Cytochrome P450 (CYP450) enzymes are critical for drug metabolism, significantly influencing pharmacokinetics, therapeutic efficacy, and potential toxicity. The prediction of CYP450 enzyme inhibition is critical in drug development, as it facilitates the identification of potential drug-drug interactions (DDIs) and the optimization of drug safety profiles. Late-stage failures in drug development are often attributed to unforeseen DDIs resulting from CYP450 inhibition, which subsequently leads to increased costs and delays in the development process. Early prediction of CYP450 inhibition can mitigate the risk of adverse effects, streamline the drug discovery pipeline, and reduce both the time and costs associated with the development of new drugs.

In this study, we developed a multi-task learning (MTL) classification model aimed at predicting the inhibition of five major CYP450 isoforms: CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Utilizing a comprehensive dataset of CYP450 inhibition data obtained from the PubChem bioassay, we implemented graph-based deep learning methodologies, including graph convolutional network (GCN) and graph attention networks (GAT), to capture molecular features at the atomic level. The MTL framework enhanced the model's capability to learn both general and specific inhibition patterns by leveraging shared information across various CYP450 tasks. The results indicate that MTL models, particularly those employing GAT, demonstrated superior performance, with area under the curve (AUC) values exceeding 0.9 across all enzymes in the external validation set. This model is anticipated to significantly enhance the early identification of CYP450 inhibition, thereby reducing the risk of drug-drug interactions and contributing to safer and more efficient drug development processes.