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Predicting Time-Concentration Profiles from Molecular Structures Using Artificial Intelligence Integrated with PBPK Modeling

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Pharmacokinetics is a critical aspect of drug development, as drug concentration profiles are directly related to therapeutic efficacy and safety. However, due to the difficulty of obtaining high-quality PK data from human subjects, most existing studies rely on animal data. This study aims to overcome these limitations by integrating artificial intelligence with Physiologically-Based Pharmacokinetic (PBPK) modeling to directly predict time-concentration profiles based on molecular structures.

Using PK-Sim, we simulated concentration profiles for 1,063 drug compounds in the brain and peripheral blood vessels over a 24-hour period following oral and intravenous administration. The key parameters required for simulations were collected from databases including ChEMBL, AQsolDB, and DrugBank. Deep learning models based on Simplified Molecular Input Line Entry System (SMILES) were developed to predict these time-concentration profiles.

The LSTM networks achieved R^2 values above 0.9 in predicting simulated time-concentration graphs based solely on molecular structure information. Additionally, when pharmacokinetic parameters such as the area under the curve (AUC), Cmax, and Tmax were extracted from the graphs, the majority of predictions fell within a 2-3 fold-change range.

This study presents a novel approach to PK prediction by generating human data through PBPK modeling and utilizing AI models to predict PK without clinical data. Future research will focus on improving model robustness and integrating pharmacodynamic predictions to further enhance the accuracy and applicability of this approach.