Integration of *in silico* structure-based and machine-learning approaches to predict drug-drug interactions

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Drug metabolizing enzymes (DME) [1] play a key role in the metabolism, elimination and detoxification of xenobiotics, drugs and endogenous molecules. While their principal role is to detoxify organisms by modifying compounds for a rapid excretion, in some cases they render their substrates more toxic thereby inducing adverse drug reactions, or their inhibition can lead to drug-drug interactions. Predicting potential inhibition of DME is important in early-stage drug discovery. We focus on Cytochrome P450 (CYP) [2] responsible for the metabolism of 90 % drugs and on sulfotransferases (SULT) [3], phase II metabolizing enzymes. We developed an original *in silico* approach for the prediction of CYP2C9 and SULT1A1 inhibition combining the knowledge of the protein structure and its dynamic behavior in response to the binding of various ligands and machine learning modeling [4]. This approach includes structural information for CYP2C9 [5] and SULT1A1 [6] based on the available crystal structures and molecular dynamic simulations (MD). We performed modeling using two learning algorithms, Support Vector Machine (SVM) and RandomForest, and we constructed combined models based on physico-chemical descriptors and predicted binding energies. Our inhibition models were able to predict CYP2C9 and SULT1A1 inhibition with an accuracy of >85% using RandomForest and > 80% using SVM on external validation sets. We validated the prediction models by in vitro inhibition tests on CYP2C9 that permitted us to discover 7 approved drugs to strongly inhibit CYP2C9.

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