[P1] Combination of structure-based and machine learning approaches for developing of selective kinase inhibitors

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Protein kinases are highly perspective drug targets since they are implicated in critical functions in signalling pathways in all cells. In many cases, the development of highly specific kinase inhibiting reagents is crucial [1]. Nevertheless, drug developments based on kinase inhibitors have been hindered by the problem of selectivity, causing numerous off-target effects. Kinase proteins' binding pockets are highly conservative structurally, which makes it a challenging task to develop inhibitors selective to a particular target against other kinases.

Based on a dataset of 109 kinase structures with bound ligands, we have calculated pocket structural similarity and sequence similarity and analyzed how these pairwise similarities were correlated with activity measurements (obtained from the PubChem BioAssay Database dataset 'Navigating the Kinome' [2]). We have found strong correlations for many kinases.

In our work, we aim to develop a method for kinase prioritization and activity prediction for designing highly-selective, novel small-molecule kinase inhibitors. We apply machine learning techniques to 3D structural descriptors of protein-ligand complexes obtained by docking and calculating several different parameters to characterize protein-ligand interactions for a given ligand conformation.

Potentially, this approach will be unbiased to ligand structural similarity to the training set compounds, which is an issue in classical QSAR methods, and will achieve high-quality prediction of novel compounds in an application of kinase-targeting drug design.

Bibliography:

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