[P10] Visually interpretable models of kinase selectivity related features derived from field-based proteochemometrics

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Protein kinases are amongst the most important drug targets as they play crucial roles in various processes such as cell growth, differentiation, apoptosis and intracellular signal transmission. Several hundred diseases are related to dysregulation of kinases[2]. Highly conserved nature of ATP binding sites poses a major challenge to design selective inhibitors for kinases. Therefore structural characterization of the ATP binding sites of kinases is an integral part in the development of more selective inhibitors/drugs.

Comparison of molecular interaction fields of binding sites within a protein family is a valuable tool to (qualitatively) interpret the selectivity of ligands[3]. A more quantitative approach to address selectivity issues of receptors is proteochemometrics, a multivariate statistics method, which aims to correlate both ligand and protein description with affinity[4]. Employing molecular interaction fields to describe proteins in combination with 2D and 3D ligand descriptors in proteochemometric models provides a way for visualizing, understanding and modifying selectivity profiles of small-molecule inhibitors.

The method is demonstrated for 50 kinases with ~2600 activity values collected from the Protein Data Bank and literature. Proteochemometric models using field-based protein descriptors, ligand descriptors and experimentally measured affinity values were generated by Partial Least Squares methods (PLS). Visual interpretation of the models with MOE highlights protein field points and ligand functional groups which influence binding affinity and selectivity.

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