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Predicting ligand binding affinity: A comparative study on the use of docking vs. Bayesian categorization and random forest recursive partitioning

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Aiming at comparing ligand-based design (LBD) and structure-based design (SBD) methods, we have carried out docking into homology models and Bayesian categorization to predict ligand binding at various human and rat nicotinic acetylcholine receptor subtypes. We found that although results vary with receptor subtype, Bayesian categorization exhibits higher accuracy and enrichment than unconstrained docking into homology models. However, docking accuracy is improved when one sets up a hydrogen-bond (HB) constraint between the cationic center of the ligand and the main-chain carbonyl group of the conserved Trp-149 or its homologue (a residue involved in cation-π interactions with the ligand basic nitrogen atom). This finding suggests that this HB is a hallmark of nicotinic ligands binding to nAChRs. We also found that ligand-based Bayesian-derived enrichment factors and structure-based docking-derived enrichment factors highly correlate to each other. Moreover, they correlate with the mean molecular fractional polar surface area of actives ligands and the fractional hydrophobic/hydrophilic surface area of the binding site, respectively. We are extending our studies by comparing LBD methods Bayesian categorization and recursive partitioning random forest with SBD docking into binding sites of proteins with experimentally-derived three-dimensional structure.

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