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High throughput in-silico screening against flexible protein receptors

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Based on the stochastic tunneling method (STUN) [1] we have developed FlexScreen [2], a novel strategy for high-throughput in-silico screening of large ligand databases. Each ligand of the database is docked against the receptor using an all-atom representation of both ligand and receptor. The ligands with the best evaluated affinity are selected as lead candidates for drug development. Using the thymidine kinase inhibitors as a prototypical example we documented [3] the shortcomings of rigid receptor screens in a realistic system. We demonstrate a gain in both overall binding energy and overall rank of the known substrates when two screens with a rigid and flexible (up to 15 sidechain dihedral angles) receptor are compared. We note that the STUN suffers only a comparatively small loss of efficiency when an increasing number of receptor degrees of freedom is considered. FlexScreen thus offers a viable compromise [4] between docking flexibility and computational efficiency to perform fully automated database screens on hundreds of thousands of ligands. We also investigate enrichment rates [5] of rigid, soft and flexible receptor models [6] for 12 diverse receptors using libraries containing up to 13000 molecules. A flexible sidechain model with flexible dihedral angles for up to 12 aminoacids increased both binding propensity and enrichment rates: EF_1 values increased by 35% on average with respect to rigid-docking (3-8 flexible sidechains). This methodology will be soon available for the Cell processor and Pipeline Pilot.

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