Semiempirical Quantum Mechanics (SQM)-based Scoring Functions for Native Protein-Ligand Pose Recognition and Virtual Screening

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General and reliable description of structures and energetics in protein-ligand binding using the docking/scoring methodology has up to now been elusive. We address this urgent deficiency of scoring functions by systematic development of corrected semiempirical quantum mechanical (SQM) methods which correctly describe all types of non-covalent interactions and are fast enough to treat systems of thousands of atoms. Two most accurate SQM methods, PM6-D3H4X and SCC-DFTB3-D3H4X, are coupled with the COSMO implicit solvation model in so called "SQM/COSMO" scoring functions and have shown unique recognition of native ligand pose in cognate docking and high enrichment in virtual screening in dozens of diverse protein-ligand systems, including challenging metalloproteins. This performance was superior to those of classical scoring functions (Glide XP, GOLD, UCSF DOCK, AutoDock 4 and AutoDock Vina). The SQM/COSMO method, due to its generality, comparability across the chemical space and no need for any system-specific parameters, gives promise to become in near future a useful computational tool in structure-based drug design and serve as a reference method for the development of other scoring functions.