CFEL SCIENCE

SEMINAR

27th November 2024 - 2:00 p.m.

CFEL-bldg. 99, seminar room IV

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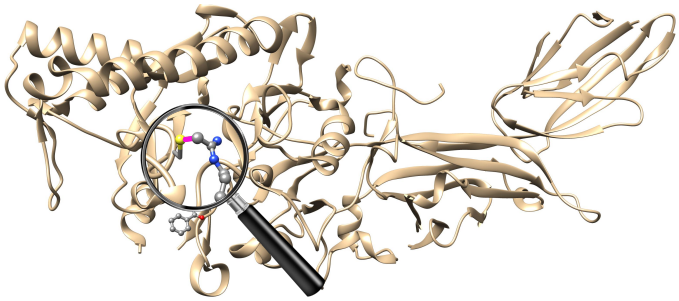
Exploring covalent ligand-protein docking with MM and QM/MM approaches

Molecular docking aims at resolving the best binding conformation of a small molecule into a protein cavity, constituting a major asset for drug discovery. Docking programs sample diverse ligand conformations and rank them with a score approximating the ligand binding free energy.



Covalent ligand-protein docking: How to accurately describe the chemical bond?

As covalent drugs show promise in targeting challenging proteins, docking codes are required to accurately model them. To this end, the Molecular Modelling Group of the Swiss Institute of Bioinformatics integrated a novel covalent procedure in its force-field based docking code, Attracting Cavities (AC). Following two-step covalent binding, the method performs the sampling with the pre-reactive topology of the ligand-protein complex, before scoring the poses with its post-reactive (bound) topology. Applied on 304 covalent ligand-protein structures, the approach yielded high success rates (78%) in reproducing ligand native binding conformations.

However, current docking codes do not adequately capture covalent bond energetics. To address this, a multiscale QM/MM procedure was implemented in AC. It estimates both noncovalent and covalent contributions to ligand binding energy at the QM level, using the CHARMM QM/MM interface with Gaussian16. This approach surprisingly diminishes the success rate compared to the classical method, suggesting potential limitations with the QM/MM embedding scheme. However, upon improvement, we expect the method to be advantageous for specific systems.

Host: Robin Santra – CFEL-DESY Theory Division