Towards Developing an Automated QM/MM Docking Suite for Quinone Reductases

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Quinone oxidoreductases belong to a class of flavin-dependent oxidoreductases, which catalyze the reduction of quinones to hydroquinones using its flavin adenosine dinucleotide (FAD) cofactor. They play pivotal roles by detoxifying the in vivo reactive oxygenated species (ROS) that damage cellular organelles, and stabilize tumor suppressor proteins. Because of these crucial functions, quinone reductases serve great promise for use in anti-tumorigenic drug development. Quinone reductases (QRs) utilize a 'ping-pong' mechanism, wherein one active site catalyzes two opposing hydride transfer reactions involving FAD. Recent studies revealed that flavin's redox state modulates the active site electrostatics and the protein dynamics.

Understanding of the opposing electrostatic and dynamic effects is crucial to successful design of molecules that can inhibit the reaction process. While many docking programs exist, it is our intent to surpass classical mechanical based programs by combining it with a quantum mechanically treated flavin ring and substrate. The hybrid quantum mechanical/classical mechanical treatment will allow a more accurate description of the electronic and dynamics effects than the traditional programs available. Using this hybrid setup combined with basic programming, one is able to calculate the free energies of binding of novel drug molecules in parallel, aiding the screening process of drug development. An overview of methodology, our highly efficient geometric docking scheme, and preliminary free energies of binding will be presented.