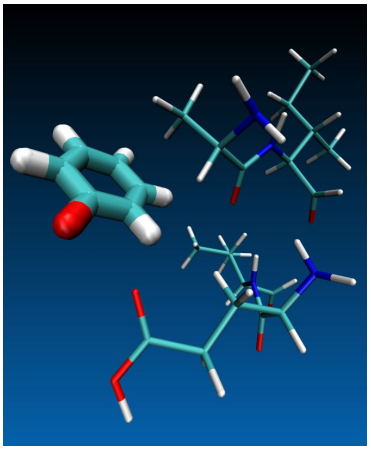
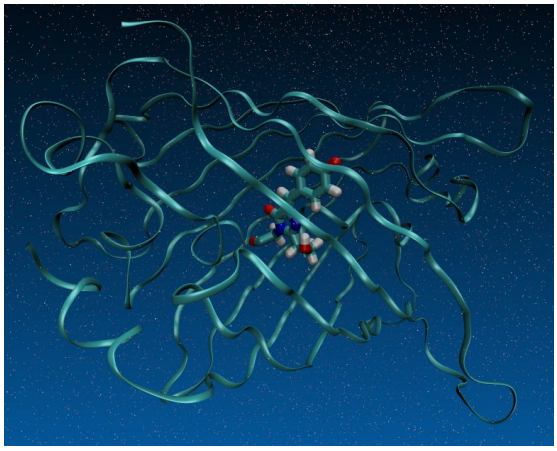
BioEFP: Extension of the Effective Fragment Potential method to biomolecules: Benchmarks and application to the Green Fluorescent Protein.

The Effective Fragment Potential (EFP) method is a computational approach designed to model intermolecular interactions and environment effects. Recently, our group formulated an extension of EFP for simulating interactions in biomolecular systems, called BioEFP. Here, we make use of a divide-and-conquer approach to fragment a large macromolecule into multiple non-covalently bonded 'effective fragments'. The parameters for these individual fragments are obtained using *ab-initio* calculations. In the polarizable QM/BioEFP simulations, the primary system of interest (namely the chromophore, and the relevant residues directly interacting with the chromophore) is described using QM, and the surrounding protein environment (including water molecules and ions) is described at polarizable embedding level, using BioEFP.

In recent benchmark studies we compared accuracy of QM/BioEFP and traditional QM/MM for electron excitation, ionization, and attachment energies in several model systems. We found that in the case of strongly polarizable systems, where charge density is localized (?) to a particular region in the system, polarizable embedding becomes essential. For instance, QM/BioEFP and QM/MM equally well predict the vertical ionization and dissociation energies in eGFP and mPlum chromophores interacting with nearby residues. However, in the case of phenolate anion interacting with T4-lysozyme system, the accuracy of QM/BioEFP simulations is significantly better as compared to conventional QM/MM simulations. We believe that the strong localization of charge density in the phenolate anion strongly polarizes the nearby amino acids, which is captured in QM/BioEFP but not in QM/MM. Currently we use the QM/BioEFP approach to understand how the protein environment influences the electronic structure, excited states and ionization potentials in the GFP protein. Our pilot findings suggest that polarization is non-negligible for accurate description of the excited state properties of GFP.





Figures: Phenolate-T4 lysozyme system (left) and green fluorescent protein (GFP; right)