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Contribution ID: **86** Type: **Invited Talk**

In-silico investigations of metal coordinating enzymes: From Biofuel production to Antimicrobial drug resistance

Wednesday, 4 December 2019 11:40 (20 minutes)

Enzymes which are directly bound to metal cofactors are referred to as Metalloenzymes. These enzymes play various biologically important roles from catalyzing electron transfer reactions to being important structural components of protein structures. Due to the abundance of metal containing enzymes and the role they play in important biological processes, it is important to study these enzymes. In-sillico approaches are readily used to study protein structure and Molecular Mechanics (MM) is an essential tool used for understanding protein dynamics. MM is used to describe protein behavior by applying a MM force field to describe bonded and nonbonded terms of a protein structure. The accuracy of the force field in describing a particular protein structure is highly dependent on the force field parameters. Unfortunately, for metalloenzymes there are no currently available force fields which can accurately describe the coordination environment of metals in metaloenzymes. As a result, performing an accurate Molecular Dynamics (MD) for metalloenzymes is extremely challenging using available force fields. To overcome this limitation Quantum Mechanics (QM) may be applied to elucidate the parameters required for accurate description of metalloenzymes during MD simulations. This approach involves the use of potential energy surface (PES) scans to evaluate the angles, bonds and dihedral parameters that are important to describe the metal binding site. Experimentally derived energy profiles generated from PES scans are then fitted using least squares fitting to a theoretical force field to generate the force field parameters. This approach three cases of metal coordinating enzymes. The first are the Auxilliary Activity family 9 (AA9) enzymes which are Cu(II) containing enzymes that have been shown to increase the rate of cellulose degradation. Secondly, new parameters were also used in the identification of novel inhibitory compounds against the Mn(II) coordinating HIV-1 reverse transcriptase enzyme. Finally, this approach was applied to the Zn(II) Bi metallic active site center of Beta lactamase enzymes which are contributors to the development of bacterial antibiotic resistance. For all three cases force field parameters were successfully generated and validated using MD simulations

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Session Classification: HPC Applications

Track Classification: Computational Chemistry