**Recent progress in DFTB driven QM/MM simulations: metal ions, polarization and machine learning**

Professor Qiang Cui (Boston University)

We’ll discuss recent progress in QM/MM simulation methodologies that are based on Density Functional Tight Binding (DFTB) as the reference potential. First, a ligand-field model is introduced to better treat the localized *d* electrons in transition metals, similar to the DFT+U model popular in materials science. Preliminary analysis using a series of Ni(II) and Ni(III) compounds and empirical +U parameters (F0/2/4 Slater integrals), we observe that the DFTB3+U model indeed provides substantial improvements over the original DFTB3 model for a number of properties, including the population and spin polarization of the *d*-shell, nature of the frontier orbitals, ligand field splitting and the energy different between low and high spin states.  Next, we discuss the issue of electronic polarization in DFTB3, for both non-covalent and metal-ligand interactions. In particular, we discuss the contribution of electronic polarization to metal binding affinity and specificity to proteins.  Finally, if time permits, we’ll briefly discuss how various machine learning techniques can be used to improve the efficiency and accuracy of QM/MM free energy simulations, such as the use of reinforcement learning to construct high-dimensional free energy surfaces and a self-supervised autoencoder to identify the key degrees of freedom in which DFTB3 differs most from high-level QM methods.