Simulating chemical reactions and redox processes in solution and in enzymes with QM/MM minimum free energy path method

Weitao Yang
Department of Chemistry, Duke University

Combined QM/MM methods provide an accurate and efficient energetic description of complex chemical and biological systems, leading to significant advances in the understanding of chemical reactions in solution and in enzymes. Ab initio QM/MM methods capitalize on the accuracy and reliability of the associated quantum mechanical approaches, however at a much higher computational cost compared with semiempirical quantum mechanical approaches. Thus reaction path and activation free energy calculations encounter unique challenges in simulation timescales and phase space sampling. Recent developments of the QM/MM minimum free energy path method overcome these challenges and enable accurate free energy determination for reaction and redox processes in solution and enzymes. Applications to several solution and enzyme reactions and redox processes will be higlighted.

On the qualitative side, we have developed an approach to detect non-covalent interactions in real space, based on the electron density and its derivatives. The intricate non-covalent interactions that govern many areas of biology and chemistry are not easily identified from molecular structure. Our approach reveals underlying chemistry that compliments the covalent structure. It provides a rich representation of van der Waals interactions, hydrogen bonds, and steric repulsion in small molecules, molecular complexes, and solids.

References

H. Hu, Z. Y. Lu, and W. T. Yang, "Qm/mm minimum free-energy path: Methodology and application to triosephosphate isomerase," Journal of Chemical Theory and Computation, vol. 3, pp. 390–406, 2007

H. Hu, Z. Y. Lu, J. M. Parks, S. K. Burger, and W. T. Yang, "Quantum mechanics/molecular mechanics minimum free-energy path for accurate reaction energetics in solution and enzymes: Sequential sampling and optimization on the potential of mean force surface," Journal of Chemical Physics, vol. 128, p. 034105, 2008

H. Hu and W. T. Yang, "Free energies of chemical reactions in solution and in enzymes with ab initio quantum mechanics/molecular mechanics methods," Annual Review of Physical Chemistry, vol. 59, pp. 573–601, 2008

H. Hu, A. Boone, and W. T. Yang, "Mechanism of omp decarboxylation in orotidine 5 '-monophosphate decarboxylase," Journal of the American Chemical Society, vol. 130, pp. 14493–14503, 2008

X. C. Zeng, H. Hu, X. Q. Hu, A. J. Cohen, and W. T. Yang, "Ab initio quantum mechanical/molecular mechanical simulation of electron transfer process: Fractional electron approach," Journal of Chemical Physics, vol. 128, p. 124510, 2008

X. C. Zeng, H. Hu, X. Q. Hu, and W. T. Yang, "Calculating solution redox free energies with ab initio quantum mechanical/molecular mechanical minimum free energy path method," Journal of Chemical Physics, vol. 130, p. 164111, 2009

E. R. Johnson, S. Keinan, Paula Mori-Sanchez, J. Contreras-Garcia, A. J. Cohen, and W. T. Yang, "Revealing Non-Covalent Interactions", J. Am. Chem. Soc., *132*, 6498, 2010.

Xiangqian Hu, Hao Hu, Jeffrey A. Melvin, Kathleen W. Clancy, Dewey G. McCafferty, and Weitao Yang, "Autocatalytic Intramolecular Isopeptide Bond Formation in Gram-Positive Bacterial Pili: A QM/MM Simulation", J. Am. Chem. Soc., *133*, 478–485, 2011.