IMPRS on Multiscale Biosystems

Embedding quantum mechanics in biomolecules

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Project description: Molecular Mechanics (MM) and Molecular Dynamics (MD) methods permit to represent efficiently the structural dynamics and interaction of biomolecules by classical force fields. In a series of important cases, however, there may be parts of a molecule that would actually require a refined description at the quantum mechanical (QM) level, while the surroundings (e.g., water molecules, neighboring amino-acid residues) cannot be disposed of, and hybrid methods must be used, where a quantum mechanical description (by density functional theory or wavefunction-based methods) is embedded into a classical description of the molecule (QM/MM methodology).

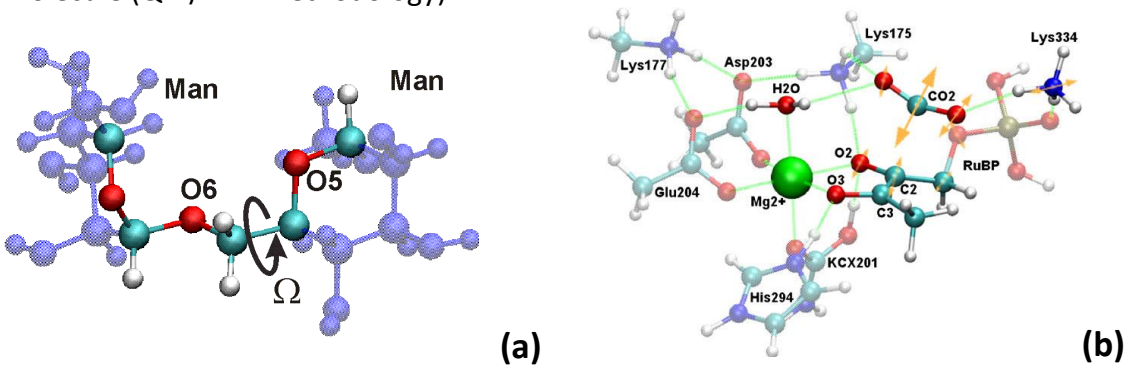

Figure 1. Two examples for potential use of QM/MM. **(a)** A disaccharide (sugar) consisting of two six rings. Rotations about the torsion angle Ω are strongly influenced by stereoelectronic effects between oxygens O5 and O6, but also by the non-trivial hydration shell around the molecule. **(b)** Uptake of CO_2 in a plant protein due to formation of a carboxy-group at RuBP, coordinated by a magnesium ion [2]. The expected motion of the carbon dioxide molecule from/to the reactive site is indicated by arrows. Shaded atoms in **(a)** and **(b)** constitute the "classical" scaffold that can be treated by efficient MM/MD methods. The inclusion of the surrounding waters amino residues into a full QM-model would render a computational approach impossible.

The goal of the project is to address some pending, intriguing problems for bio-molecular systems (see two examples in **Figure 1**), such as torsions around difficult glycosidic linkages **(a)**, or "true" reactions such as the carboxylation step in the Calvin cycle of photosynthesis **(b)**. Typically these processes involve transitions between distinct states, and not only their equilibrium is of importance, but also the path connecting them, the kinetics of the reaction. A detailed exploration of the energy landscape for such a multi-scale problem is prohibitively expensive. Recently, various new sampling strategies have been suggested that could render the QM/MM problem much more accessible, such as biased dynamics (see [1] and references therein), pushing the system out of deep energetic traps, or transition path sampling [3], where probable reaction paths are distilled from a whole ensemble of paths.

The student will gradually learn how to implement these new sampling techniques efficiently, and to integrate and use them in a QM/MM setting.

References:

1. Wehle, M.; Vilotijevic, I.; Lipowsky, R.; Seeberger, P. H.; Varon Silva, D.; Santer, M.: accepted at JACS, http://dx.doi.org/10.1021/ja302803r
2. J. Götze and P. Saalfrank, Quantum chemical modeling of the kinetic isotope effect of the carboxylation step in RuBisCO, *J. Mol. Modeling* vol. **18**, pp. 1877 (2012)
3. W. Li and F. Gräter, Atomistic Evidence of How Force Dynamically Regulates Thiol/Disulfide Exchange. J. Am. Chem. Soc., vol. 132, pp. 16790 (2010)

Required background: The prospective student should have a general interest in computational methods in chemistry or physical chemistry, and some background in physics or physical chemistry.

Paper to read before the interview: Reference 3.

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