Abstract:

Obtaining A Dynamic Picture of Biological Carbon Fixation by Computational Spectroscopy and Simulations

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Biological carbon fixation converts CO_2 to organic compounds that are key to the cellular metabolism. Given the central role of CO_2 in global warming and a general interest in generating value-added chemicals from C1 compounds, carbon fixation represents an important concept in green and sustainable chemistry. In nature, this process can be accomplished by a complex of two metalloenzymes, carbon-monoxide dehydrogenase (CODH) and acetyl-CoA synthase (ACS). The key processes of CO_2 reduction (CODH) and CO methylation (ACS) are catalyzed by two nickel-containing protein-embedded metal clusters. Reaction intermediates of these two clusters can be isolated, and vibrational spectroscopies, especially advanced nonlinear techniques, are valuable tools for studying their structural and dynamical properties. Computational modelling is necessary, though, to understand the information encoded in the spectroscopic data. Guided by two groups with expertise in advanced spectroscopy and biomolecular modelling, the successful candidate will utilize computational tools, including quantum-classical dynamics simulations, to comprehensively predict vibrational spectroscopic properties of CODH and ACS and understand the structure, dynamics, and mechanisms of these enzymes.

Extended description version of the project:

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1. Overall goal of the project

The overall goal of the project is to **understand the structural and dynamical properties** of CODH and ACS, thereby elucidating key determinants of biological CO_2 and CO activation. This approach promises to reveal sustainable routes to carbon sequestration and the formation of C2 compounds. Necessary **insights into catalytic intermediates can be obtained by vibrational spectroscopy** since intermediates of CODH and ACS feature metal-bound CO and CO_2. Experimental spectra are often difficult to interpret, though, especially for advanced nonlinear techniques like two-dimensional infrared (2D-IR) spectroscopy, which yields otherwise inaccessible insights into structural details and molecular dynamics. **Simulating vibrational properties is a powerful approach for understanding experimental spectra.** However, for complex metalloenzymes like CODH and ACS, this approach requires an adequate modelling of metal cofactors and their protein environment, and 2D-IR spectra cannot be simulated using standard methods. Instead, an anharmonic representation of the potential energy surface (PES) is required, and the influence of dynamics on spectroscopic properties must be modelled. Hence, this project will **(1) develop an advanced computational toolbox** for simulating static and dynamic aspects of linear and nonlinear vibrational spectra of metalloenzymes and **(2) apply it to structural and mechanistic key question about CODH and ACS.**

2. State of the art

CODH and ACS have been extensively studied by biochemical techniques, and **crystal structures are available**, also for substrate-bound states.[1,2] These crystal structures represent a basis for the planned computational studies. **Various spectroscopic experiments have also been performed.** This includes vibrational studies, employing conventional IR absorption and resonance Raman (RR) spectroscopies. **Most recent vibrational spectroscopic work has been published by members of UniSysCat**, including the Mroginski group.[3,4] These studies have elucidated structural and mechanistic aspects of CODH by analyzing spectroscopic properties of enzyme incubated with NCO^- and CN^-. **IR absorption spectra were modelled and interpreted** within the harmonic limit by a quantum-classical (QM/MM) hybrid approach. **Further experiments on CODH and ACS are planned** in UniSysCat, including ultrafast nonlinear (2D-IR) experiments by the Horch group.[5]

Static linear vibrational spectra can be modelled using harmonic normal mode analysis. This approach is used on a routine basis in the Horch and Mroginski groups. If the **impact of dynamics on linear spectra** (lineshapes) is relevant, vibrational spectra can be alternatively obtained by Fourier transforms of dipole (IR) or polarizability (Raman) autocorrelation functions.[6] These calculations require molecular dynamics (MD) simulations using either classical or QM force fields, but they do not yield explicit insights into dynamics as these are not resolved in linear spectra. **Static nonlinear 2D-IR spectra** can be modelled, e.g., by using second-order vibrational perturbation theory (VPT2) employing a quartic (anharmonic) expansion of the PES.[7] The feasibility and relevance of this approach

for simulating 2D-IR spectra of complex biological metal centers containing CO and CN^- ligands has been demonstrated by the Horch group.[8] **Simulating dynamic aspects of 2D-IR spectra** can be accomplished by evaluating the third-order optical response function (or its classical analogue) for a set of fluctuating oscillators.[9] The exact procedure depends on the system of interest and the studied aspects. While a mixed quantum-classical approach utilizing empirically parametrized model Hamiltonians (and classical MD trajectories) has been widely used, a model-free approach employing the classical response function (and QM/MM dynamics trajectories) has also been introduced.

3. Specific aims and how they may be reached

The initial phase is dedicated to **model building**. This includes the choice of relevant and vibrationally accessible intermediates (e.g. CO_2 and $(CO)_2$ adducts of CODH and ACS, respectively)[1,10] and the set-up of computational models including the definition of QM and MM layers for hybrid calculations. Special emphasis will be placed on the impact of the protein environment and strategies to explore it systematically, based on protocols previously developed in the Mroginski group.[3,4,11] Subsequently, adequate **electronic structure methods need to be explored**, including the level theory required to model the catalytic metal sites and their interaction with the protein as well as the possible broken-symmetry states of FeS cluster moieties. Once the structural features are well reproduced, **static linear vibrational spectra will be calculated** within the harmonic limit (IR absorption and Raman) for comparison with and interpretation of experimental data. The next steps of the project will focus on the **simulation of static nonlinear vibrational spectra** (especially 2D-IR) within the VPT2 framework. Given the high accuracy required for these calculations, a refinement of the computational models and utilization of reduced dimensionality schemes may be necessary.[8] Simulated spectra will be systematically analyzed with respect to structural and electronic factors that govern the spectroscopic observables.[8] Knowledge gained by static calculations will be subsequently utilized to **develop strategies for simulating molecular dynamics and its impact on spectroscopic properties**. This will utilize QM/MM dynamics simulations that guarantee an accurate and unbiased description of CODH and ACS metal-site dynamics, without the need of force-field parametrization. The **impact of dynamics on linear vibrational spectra** will then be evaluated as described above. Finally, in the most challenging part of the project, **different approaches for simulating nonlinear vibrational spectra** will be explored (*vide supra*). These endeavors will focus on 2D-IR spectroscopy and the wealth of dynamic information included in time series of such spectra.

Work in the project will be tightly linked to experimental studies and, if suitable, the successful candidate may be involved in parts of this work. This includes nonlinear (2D-IR) studies in the Horch group as well as conventional IR and RR studies performed in the groups of Zebger and Hildebrandt. The planned studies are also linked to work in the Dobbek group (X-ray crystallography and biochemistry of CODH and ACS) and other computational work in the Mroginski group. High-performance-computing facilities and required software are available at the supervisors' host institutions.

References

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