Master 2 research internship in Integrated Structural & Cell Biology in Grenoble

Supervisor(s):
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Host laboratory:
LCBM, COMX team
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Title of the M2 research internship:
Understanding substrate binding pathways in biological nitrogen fixation via multiscale modelling

Project summary:
Nitrogenases are Nature‘s solution to fixing dinitrogen, making it available for incorporation into biomolecules. To perform this complex chemical transformation: Nature utilizes a complex machine consisting of two bacterial metalloproteins (MoFe and Fe protein) and 3 iron-sulfur clusters (F-cluster, P-cluster, FeMoco) that catalyze the reaction: N2 + 8e- + 8H+ +16MgATP => 2NH3 + H2 + MgADP + Pi
Little is known about the details of substrate and product pathways within MoFe protein, electron and proton transfer between proteins as well as the precise binding site of N2. Additionally the nature of the protein-protein interaction between MoFe protein and Fe protein and how that binding activates the the unusual deficit-spending electron-transfer mechanism is not understood.
In previous work we have performed detailed active site QM/MM multiscale modelling of the MoFe protein, taking a local focus in unravelling the electronic aspects of the cofactor that is responsible for the reactivity and substrate binding and reduction of N2 to ammonia.
In this project, we propose to go beyond this local static approach and instead explore the more global aspects and the dynamic nature of MoFe protein and it‘s interaction with the Fe protein. We will perform classical simulations of MoFe protein and in the MoFe:Fe complex in explicit solvent, adding in a small concentration of N2 gas and explore if we can unravel the pathways for how N2 and other substrates enter the MoFe protein (with and without Fe protein bound). We will use a combination of direct classical MD simulations as well as biased dynamics simulations (umbrella sampling, metadynamics) to accomplish this.
Depending on the proficiency of the student, we will either perform the simulations using ASH, a multiscale modelling program developed in our research group (https://ash.readthedocs.io) or via the established GROMACS program. An atomistic model of MoFe protein is available.

Keywords:
multiscale modelling, bacterial metalloprotein, biological nitrogen fixation

Relevant publications of the team:
Moco, B. Benediktsson, R. Bjornsson* Analysis of the geometric and electronic structure of spin-coupled iron-sulfur dimers with broken-symmetry DFT: implications for Fe J. Chem. Theory Comput. 2022, accepted.

N. B. Spiller, R. Bjornsson*, S. DeBeer, F. Neese, Carbon Monoxide Binding to the Iron-Molybdenum Cofactor of Nitrogenase: A Detailed Quantum Mechanics/Molecular Mechanics Investigatio Inorg. Chem. 2021, 60, 18031-18047.

A. Th. Thorhallsson, R. Bjornsson, The E2 state of FeMoco: hydride formation vs. Fe reduction and a mechanism for H2 evolution Chem. Eur. J. 2021, 27, 16788-16800.

B. Benediktsson, R. Bjornsson*, QM/MM Study of Resting State Vanadium Nitrogenase: Molecular and Electronic Structure of the Iron, Vanadium Cofacto Inorg. Chem. 2020, 59, 11514–11527.

C. Van Stappen, L. Decamps, G. E. Cutsail III, R. Bjornsson, J. Henthorn, J. A. Birrell and S. DeBeer, The Spectroscopy of Nitrogenases Chem. Rev. 2020, 120, 5005–5081.

A. Th. Thorhallsson, B. Benediktsson, R. Bjornsson* A model for dinitrogen binding in the E4 state of nitrogenase. Chem. Sci. 2019, 10, 11110-11124.

C. Van Stappen, A. Th. Thorhallsson, L. Decamps, R. Bjornsson*, S. DeBeer* Resolving the structure of the E1 state of Mo Nitrogenase through Mo and Fe K-edge EXAFS and QM/MM calculations Chem. Sci. 2019, 10, 9807-9821.

B. Benediktsson, A. T. Thorhallsson, R. Bjornsson*, QM/MM calculations reveal a bridging hydroxo group in a vanadium nitrogenase crystal structure Chem. Comm., 2018, 54, 7310-7313.

B. Benediktsson and R. Bjornsson*, QM/MM Study of the Nitrogenase MoFe Protein Resting State: Broken-Symmetry States, Protonation States, and QM Region Convergence in the FeMoco Active Site Inorg. Chem. 2017, 56, 13417-13429.