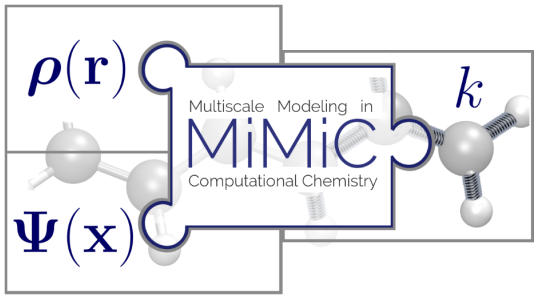
Multiscale Molecular Dynamics with MiMiC



July 18 - 22 2022
CECAM-HQ-EPFL, Lausanne, Switzerland

Jógvan Magnus Haugaard Olsen
Technical University of Denmark, Denmark

Ursula Roethlisberger
EPFL, Switzerland

Simone Meloni
University of Ferrara, Italy

1. Description

The school focuses on the modeling of large and complex (bio)chemical systems, ranging from molecules in solution to membrane-embedded proteins. The large size of such systems and the long-time scale of chemically relevant phenomena necessitates the use of a combination of complementary techniques allowing to span multiple temporal and spatial scales. The school is aimed at young and more experienced researchers who will be taught advanced simulation techniques including multiscale and rare event sampling methods. The school covers methods for coupling different spatial resolutions using hybrid quantum mechanics/molecular mechanics (QM/MM) models [1] and multiple time scales through multiple time step (MTS) algorithms [2] as well as sampling methods for reconstructing free energy surfaces, identifying reaction paths, and computing process/reaction rates [3]. The theoretical lectures will be complemented by practical sessions where the multiscale modeling framework MiMiC [4-6] will be used. This also includes training in the efficient use of HPC resources, e.g., how to setup a simulation to optimize efficiency.

Key References

*[1] E. Brunk, U. Rothlisberger, Chem. Rev., **115**, 6217 (2015)*
*[2] E. Liberatore, R. Meli, U. Rothlisberger, J. Chem. Theory Comput., **14**, 2834 (2018)*
*[3] S. Bonella, S. Meloni, G. Ciccotti, Eur. Phys. J. B, **85**, 97 (2012)*
*[4] J. Olsen, V. Bolnykh, S. Meloni, E. Ippoliti, M. Bircher, P. Carloni, U. Rothlisberger, J. Chem. Theory Comput., **15**, 3810 (2019)*
*[5] V. Bolnykh, J. Olsen, S. Meloni, M. Bircher, E. Ippoliti, P. Carloni, U. Rothlisberger, J. Chem. Theory Comput., **15**, 5601 (2019)*
[6] MiMiC: A Framework for Multiscale Modeling in Computational Chemistry - https://mimic-project.org/

2. Program

Day 1 - Monday July 18th 2022

- 08:45 to 09:00 - Welcome & Introduction
- 09:00 to 09:45 - Introduction to QM/MM
- 09:45 to 09:55 - Short break
- 09:55 to 10:40 - Computer architectures and parallelization
- 10:40 to 11:05 - Coffee break
- 11:05 to 11:50 - Introduction to MiMiC
- 11:50 to 12:00 - Short break
- 12:00 to 12:30 - Preparation for tutorials
- 12:30 to 14:00 - Lunch
- 14:00 to 15:45 - Tutorials
- 15:45 to 16:15 - Coffee break
- 16:15 to 18:00 - Tutorials

Day 2 - Tuesday July 19th 2022

- 09:00 to 09:45 - Advanced topics in QM/MM (part one)
- 09:45 to 09:55 - Short break
- 09:55 to 10:40 - Advanced topics in QM/MM (part two)
- 10:40 to 11:05 - Coffee break
- 11:05 to 11:50 - Advanced topics in QM/MM (part three)
- 11:50 to 12:00 - Short break
- 12:00 to 12:30 - Example QM/MM applications / preparation for tutorials
- 12:30 to 14:00 - Lunch
- 14:00 to 15:45 - Tutorials
- 15:45 to 16:15 - Coffee break
- 16:15 to 18:00 - Tutorials

Day 3 - Wednesday July 20th 2022

- 09:00 to 09:45 - Constraints and multiple time step algorithms
- 09:45 to 09:55 - Short break
- 09:55 to 10:40 - Multiple time step integrators for multilevel QM and QM/MM MD
- 10:40 to 11:05 - Coffee break
- 11:05 to 11:50 - Machine learning techniques for QM and QM/MM MD
- 11:50 to 12:00 - Short break
- 12:00 to 12:30 - Example QM/MM applications / preparation for tutorials
- 12:30 to 14:00 - Lunch
- 14:00 to 15:45 - Tutorials
- 15:45 to 16:15 - Coffee break
- 16:15 to 17:45 - Tutorials
- 18:00 to 20:00 - Poster session & aperitif

Day 4 - Thursday July 21st 2022

- 09:00 to 09:45 - Force matching QM/MM MD
- 09:45 to 09:55 - Short break
- 09:55 to 10:40 - Introduction to rare event techniques
- 10:40 to 11:05 - Coffee break
- 11:05 to 11:50 - Modern sampling methods in configuration and trajectory space
- 11:50 to 12:00 - Short break
- 12:00 to 12:30 - Example QM/MM applications / preparation for tutorials
- 12:30 to 14:00 - Lunch
- 14:00 to 15:45 - Tutorials
- 15:45 to 16:15 - Coffee break
- 16:15 to 18:00 - Tutorials
- 19:30 to 22:00 - Social dinner

Day 5 - Friday July 22nd 2022

- 10:00 to 10:30 - Excited state QM/MM MD
- 10:30 to 11:00 - Coffee break
- 11:00 to 11:30 - Example QM/MM applications
- 11:30 to 11:45 - Closing Word
- 11:45 to 13:00 - Lunch
- 13:00 to 17:00 - Tutorials / discussion / bring your own project (optional)

3. Abstracts

Advanced topics in QM/MM

Jógvan Magnus Haugaard Olsen
Technical University of Denmark, Denmark

In these lectures, we go through some of the more advanced topics in QM/MM. This includes additive and subtractive schemes, bonded and non-bonded interactions, approaches to deal with covalent bonds that cross the QM–MM boundary, choice of QM and MM methods, size of the QM subsystem, electron spill-out, and more. We will also discuss aspects that are related to the MiMiC-based implementation of QM/MM.

*[1] H. Senn, W. Thiel, Angew. Chem. Int. Ed., **48**, 1198 (2009)*
*[2] E. Brunk, U. Rothlisberger, Chem. Rev., **115**, 6217 (2015)*
*[3] J. Olsen, V. Bolnykh, S. Meloni, E. Ippoliti, M. Bircher, P. Carloni, U. Rothlisberger, J. Chem. Theory Comput., **15**, 3810 (2019)*
*[4] V. Bolnykh, J. Olsen, S. Meloni, M. Bircher, E. Ippoliti, P. Carloni, U. Rothlisberger, J. Chem. Theory Comput., **15**, 5601 (2019)*

Computer architectures and parallelization

Davide Mandelli
FZJ, Germany

In this lecture, we will introduce basic concepts of high-performance computing (HPC). This includes an overview of methods aimed at maximizing single-thread performance, an introduction to the concept of parallel computing, and of strategies used to achieve high code scalability.

[1] V. Bolnykh, PhD Thesis: 'Massively parallel quantum mechanical/molecular mechanical interface', RWTH Aachen University (2019)
*[2] V. Bolnykh, U. Rothlisberger, P. Carloni, Isr. J. Chem., **60**, 694 (2020)*
*[3] V. Bolnykh, G. Rossetti, U. Rothlisberger, P. Carloni, WIREs. Comput. Mol. Sci., **11** (2021)*

Constraints and multiple time step algorithms

Davide Mandelli
FZJ, Germany

In the first part of this lecture, we will discuss standard algorithms used to enforce constraints in molecular dynamics simulations. We will then review the Liouville formulation of time-reversible integration schemes and present a general derivation of multiple time step algorithms.

*[1] J. Ryckaert, G. Ciccotti, H. Berendsen, Journal of Computational Physics, **23**, 327 (1977)*
*[2] G. Ciccotti, J. Ryckaert, Computer Physics Reports, **4**, 346 (1986)*
*[3] Y. Weinbach, R. Elber, Journal of Computational Physics, **209**, 193 (2005)*
*[4] H. Andersen, Journal of Computational Physics, **52**, 24 (1983)*
*[5] G. Martyna, M. Tuckerman, D. Tobias, M. Klein, Molecular Physics, **87**, 1117 (1996)*
[6] D. Frenkel and B. Smit, 'Understanding Molecular Simulations', Academic Press, San Diego (2002)

Example QM/MM applications: "Application of MiMiC to biomolecular systems"

Paolo Carloni
Forschungszentrum Jülich & RWTH Aachen University, Germany

The talk will illustrate some of the first large-scale biophysical applications of MiMiC, with a focus on ion channels and transporters.

*[1] M. Chiariello, V. Bolnykh, E. Ippoliti, S. Meloni, J. Olsen, T. Beck, U. Rothlisberger, C. Fahlke, P. Carloni, J. Am. Chem. Soc., **142**, 7254 (2020)*

Example QM/MM applications: "Oxidative damage affects redox properties of DNA"

Sophia Johnson
EPFL, Switzerland

A brief overview of QM/MM simulations to measure redox changes in DNA systems under oxidative stress both in unraveled and wound DNA structures. We discuss how we evaluate the validity of a proposed charge-transfer mechanism for DNA damage recognition through the application of Marcus theory of electron transfer and Washel's theory of vertical energy gap distributions.

*[1] P. Diamantis, I. Tavernelli, U. Rothlisberger, J. Chem. Theory Comput., **16**, 6690 (2020)*
*[2] A. Warshel, J. Phys. Chem., **86**, 2218 (1982)*
*[3] R. Marcus, The Journal of Chemical Physics, **24**, 966 (1956)*

Excited state QM/MM MD

Ursula Roethlisberger
EPFL, Switzerland

In this lecture, we discuss the implementation of QM/MM methods in the context of adiabatic and nonadiabatic dynamics in electronically excited states.

*[1] E. Brunk, U. Rothlisberger, Chem. Rev., **115**, 6217 (2015)*

Force matching QM/MM MD

Ursula Roethlisberger
EPFL, Switzerland

In this lecture, we discuss how the force matching method can be applied to generate force fields directly from QM or QM/MM MD simulations.

*[1] F. Ercolessi, J. Adams, Europhys. Lett., **26**, 583 (1994)*
*[2] A. Laio, S. Bernard, G. Chiarotti, S. Scandolo, E. Tosatti, Science, **287**, 1027 (2000)*
*[3] P. Maurer, A. Laio, H. Hugosson, M. Colombo, U. Rothlisberger, J. Chem. Theory Comput., **3**, 628 (2007)*
*[4] M. Doemer, P. Maurer, P. Campomanes, I. Tavernelli, U. Rothlisberger, J. Chem. Theory Comput., **10**, 412 (2013)*

Introduction to MiMiC

Jógvan Magnus Haugaard Olsen
Technical University of Denmark, Denmark

This lecture will give an overview of the MiMiC framework. This includes a short introduction to its basic components, communication and parallelization models, and also some practicalities.

*[1] J. Olsen, V. Bolnykh, S. Meloni, E. Ippoliti, M. Bircher, P. Carloni, U. Rothlisberger, J. Chem. Theory Comput., **15**, 3810 (2019)*
*[2] V. Bolnykh, J. Olsen, S. Meloni, M. Bircher, E. Ippoliti, P. Carloni, U. Rothlisberger, J. Chem. Theory Comput., **15**, 5601 (2019)*

Introduction to QM/MM

Simone Meloni
University of Ferrara, Italy

In this lecture, we introduce the basics of the QM/MM method. This includes a motivation for the use of QM/MM, i.e., why and when should we use QM/MM, and an illustration of the workflow leading to a QM/MM MD simulation.

Introduction to rare event techniques

Simone Meloni
University of Ferrara, Italy

In this lecture, we introduce fundamental theories for the calculation of rates of chemical reactions and physical processes. We will introduce key quantities such as (Landau) free energy and committor.

*[1] P. Bolhuis, D. Chandler, C. Dellago, P. Geissler, Annu. Rev. Phys. Chem., **53**, 291 (2002)*
*[2] E. Vanden-Eijnden, F. Tal, The Journal of Chemical Physics, **123**, 184103 (2005)*
*[3] S. Bonella, S. Meloni, G. Ciccotti, Eur. Phys. J. B, **85**, 97 (2012)*

Machine learning techniques for QM and QM/MM MD

Ursula Roethlisberger
EPFL, Switzerland

In this lecture, a kernel-based machine learning model is introduced to predict energies and nuclear forces in QM- and QM/MM-based molecular dynamics simulations.

*[1] A. Christensen, F. Faber, O. von Lilienfeld, J. Chem. Phys., **150**, 064105 (2019)*
*[2] F. Mouvet, J. Villard, V. Bolnykh, U. Rothlisberger, Acc. Chem. Res., **55**, 221 (2022)*

Modern sampling methods in configuration and trajectory space

Simone Meloni
University of Ferrara, Italy

Rate calculations require one to compute quantities such as free energy barriers (see previous lecture). Relative stability between the initial and final states of a process requires computation of the difference of free energy between the two states. Sometimes, other possible states of the system at hand are unknown, and must be identified in the first place. In this lecture, some of the techniques developed to deal with these problems will be discussed, and some of them will be used in the exercise session.

*[1] S. Bonella, S. Meloni, G. Ciccotti, Eur. Phys. J. B, **85**, 97 (2012)*
*[2] A. Barducci, G. Bussi, M. Parrinello, Phys. Rev. Lett., **100**, 020603 (2008)*
*[3] A. Laio, M. Parrinello, Proc. Natl. Acad. Sci. U.S.A., **99**, 12562 (2002)*
*[4] G. Ciccotti, M. Ferrario, Molecular Simulation, **30**, 787 (2004)*

Multiple time step integrators for multilevel QM and QM/MM MD

Ursula Roethlisberger
EPFL, Switzerland

In this lecture, we will discuss how multiple time step integrators can be applied in the context of multilevel QM and mixed QM/MM molecular dynamics simulations to increase performance.

*[1] E. Liberatore, R. Meli, U. Rothlisberger, J. Chem. Theory Comput., **14**, 2834 (2018)*
*[2] P. Baudin, F. Mouvet, U. Rothlisberger, J. Chem. Phys., **156**, 034107 (2022)*
*[3] F. Mouvet, J. Villard, V. Bolnykh, U. Rothlisberger, Acc. Chem. Res., **55**, 221 (2022)*

4. Posters

Efficient implementation of isotropic cubic response functions for two-photon absorption cross sections within the self-consistent field approximation

Karan Ahmadzadeh, Mikael Scott, Manuel Brand, Olav Vahtras, Xin Li, Zilvinas Rinkevicius, Patrick Norman
KTH, Sweden

Within the self-consistent field approximation, computationally tractable expressions for the isotropic second-order hyperpolarizability have been derived and implemented for the calculation of two-photon absorption cross sections. The novel tensor average formulation presented in this work allows for the evaluation of isotropic damped cubic response functions using only ∼3.3 % (one-photon off-resonance regions) and ∼10% (one-photon resonance regions) of the number of auxiliary Fock matrices required when explicitly calculating all the needed individual tensor components. Numerical examples of the two-photon absorption cross section in the one-photon off-resonance and resonance regions are provided for alanine–tryptophan and 2,5-dibromo-1,4-bis(2-(4-diphenylaminophenyl)vinyl)-benzene. Furthermore, a benchmark set of 22 additional small- and medium-sized organic molecules are considered. In all these calculations, a quantitative assessment is made of the reduced and approximate forms of the cubic response function in the one-photon off-resonance regions and results demonstrate a relative error of less than ∼5% when using the reduced expression as compared to the full form of the isotropic cubic response function

Exploring the role of metals in the activity of enzymes involved in diseases

Angela Parise[1], Aurelien de la Lande[2], Tiziana Marino[3], Alessandra Magistrato[1]
[1]Scuola Internazionale Superiore di Studi Avanzati - SISSA, Italy
[2]Université Paris-Saclay, France
[3]Università della Calabria, Italy

Metal ions play an important role in the biological function of many enzymes. The nature of the metal and the way in which it interacts with the protein and other cofactors result in their functionality as electron donors/acceptors, Lewis acids or structural enhancers. This contribution is divided into two parts, as described below.

- The first part is dedicated to human *Viperin* (*Virus inhibitory protein, endoplasmic reticulum-associated, interferon-inducible*) which catalyses conversion reaction of cytidine triphosphate (CTP) to 3'-deoxy-3',4'-didehydro-CTP (ddh-CTP), a molecule that demonstrates antiviral properties. The activation reaction is by electron transfer (ET) on 4Fe-4S cluster present in the active site. A structural and dynamics investigation of viperin through Molecular Dynamic simulations was perfoed complemented by QM/MM calculations, based on constrained-DFT for the QM part, to clarify the favored spin configuration of the Fe-S cluster. All six possible antiferromagnetically coupled spin states (ααββ, αβαβ, αβα, ββαα, βαβα, βααβ) were explored. The decoupled hypothesis QM+MM^{pol} simplified scheme in the Marcus Theory framework was used to valuate the ionization potential of the 4Fe-4S cofactor. [1]
- A catalytic Mg^{2+} ion is instead present to all small GTPases. These proteins that exert their function by acting as molecular switches, being activated by a guanosine triphosphate (GTP) binding, and being deactivated upon GTP hydrolysis. This cycle is fostered by the GTPase-activating protein (GAP), and by the guanine exchange factor (GEF) proteins, which enhance the exchange of the GTP/GDP nucleotide during the cycle. Rho GTPase signaling contributes to all hallmarks of cancer and emerges as a novel therapeutic target. [2] In this project we aim to investigate the molecular basis of GTP hydrolysis as mediated by a Mg^{2+} ion in a prototypical and highly oncogenic Rac1 and RhoA GTPases. Complementarily, all-atoms simulations will be performed to disclose the molecular terms of small-GTPases interactome in health and disease. This will be done to devise novel anti-cancer strategies that interfere with signalling processes regulated by small GTPases. In the present contribution, the preliminary results and our perspectives are reported.

*[1] X. Wu, J. Hénin, L. Baciou, M. Baaden, F. Cailliez, A. de la Lande, Front. Chem., **9** (2021)*
*[2] J. Xu, F. Simonelli, X. Li, A. Spinello, S. Laporte, V. Torre, A. Magistrato, J. Chem. Inf. Model., **61**, 2967 (2021)*

Investigation of hydrogen peroxide and dioxygen mechanism in lytic polysaccharide monooxygenase

Marlisa M. Hagemann, Erik D. Hedegård
University of Southern Denmark (SDU), Denmark

Lytic polysaccharide monooxygenases (LPMOs) are copper-dependent metalloenzymes that use oxidative chemistry to break down polysaccharides. Hence, they can significantly increase the efficiency of sustainable biofuel generation from abundant polysaccharides, such as cellulose. However, the precise molecular mechanism and the true nature of the co-substrate remain controversial. Most LPMOs target insoluble polysaccharide substrates, which complicates many experimental methods. Thus, the investigation of the LPMOs mechanism can benefit tremendously from theoretical methods.
Only a small number of theoretical studies have addressed the mechanism of LPMOs. A recent theoretical study by Hedegård and Ryde [1] investigated the full mechanism for a substrate-LPMO complex considering two potential co-substrates, H_2O_2 and O_2. However, in this study rather small QM regions were employed, and it is known that reaction energies calculated for enzymes can be very sensitive to the size of the QM region.[2]
Here, we recalculated the early reaction pathways for the two potential co-substrates, H_2O_2 and O_2. Our calculations are based on the previous study [1], using QM/MM in combination with density functional theory. For more accurate energetics, we extended the QM region by two second-sphere residues and two water molecules close to the active site. In addition to the previous suggested paths, we considered several additional intermediates and attempted to calculate the initial binding energy of the two co-substrates to the LPMO for the first time.
This work demonstrates the importance of a well-considered QM region, and we were able to use the results to determine the influence of the surrounding amino acids. Our conclusions for the mechanism agree with recent experimental data and computational studies, but also highlight pitfalls and limitations of the methods used.

*[1] E. Hedegård, U. Ryde, Chem. Sci., **9**, 3866 (2018)*
*[2] S. Sumner, P. Söderhjelm, U. Ryde, J. Chem. Theory Comput., **9**, 4205 (2013)*

Mismatching versus matching nucleotides in polymerases investigated using free energy perturbation

David Figueroa, Pietro Vidossich, Marco De Vivo
Italian Institute of Technology, Italy

Polymerases (Pol) catalyze RNA or DNA synthesis by the addition of ribonucleoside triphosphate (NTP) or deoxyribonucleoside triphosphate (dNTP), respectively, using a template strand. These enzymes have a central role in several crucial processes such as repair, translation and replication of genetic material. The wide range of processes in which they are involved makes these enzymes promising targets for drug discovery, as well as for biotechnological applications.
Two fundamental properties characterize Pol catalysis: fidelity and processivity. The former is defined as the ability of inserting the correct Watson-Crick nucleotide in the nascent DNA or RNA strand. The latter concerns the number of nucleotides inserted during a single binding event of the DNA and the protein. Pols display varying levels of fidelity and processivity, which are ultimately governed by interactions at the molecular level, suggesting that Pols may be engineered to control the balance between fidelity and processivity.
Specifically, the fidelity in polymerases is associated to the catalytic efficiency, which is directly related with the binding energy of the incoming dNTP (K_d) and the turn over number (k_{cat}) in the catalyzed reaction. Quantification of these two aspects is crucial for the understanding of polymerase mechanisms and for future design of engineered variants. Alchemical free energy calculations (FEP) are a suitable methodology for the estimation of binding energies. Therefore, we explored how FEP may be used to quantify relative changes in binding free energies of mismatching versus matching (Watson – Crick) nucleotides in Pol β, a polymerase specialized in DNA repair, for which available crystal structures of ternary complexes and steady state kinetics measurements may serve for validation.

*[1] S. Filges, E. Yamada, A. Ståhlberg, T. Godfrey, Sci. Rep., **9**, 3503 (2019)*
*[2] I. Geronimo, P. Vidossich, E. Donati, M. Vivo, WIREs. Comput. Mol. Sci., **11** (2021)*

Modelling and simulations of DNA translocation in polymerases eta investigated using enhanced sampling methods

Alessia Visigalli, Pietro Vidossich, Marco De Vivo
Istituto Italiano di Tecnologia, Italy

Polymerases are enzymes responsible for nucleic acid replication, transcription and repair, and thus very important for both pharmacological and biotechnological applications [1][2]. Their activity is mainly characterized by two key properties: fidelity [1][2], which is the ability to duplicate the nucleic acid faithfully and processivity [2], which is the ability to carry out continuous synthesis without frequent dissociation of the polymerase from the nucleic acid. While the former property has been addressed by numerous computational studies in different systems [1], the latter remains largely unclear from a mechanistic point of view. This is because of the inherent difficulties in modeling at the atomistic level the two competitive processes involved: protein/nucleic acid dissociation and translocation of the polymerase along the nucleic acid strand [3][4]. The use of enhanced sampling techniques allows the observation of rare events [5], such as the translocation of polymerases, in computationally accessible timescales. However, the choice of suitable collective variable which capture the slow modes of the process is often a considerable challenge [6]. Here, we report on our efforts in modeling the polymerase /DNA translocation by the combination of statistical analysis and machine learning techniques [7].

*[1] I. Geronimo, P. Vidossich, M. De Vivo, ACS Catal., **11**, 14110 (2021)*
*[2] I. Geronimo, P. Vidossich, E. Donati, M. Vivo, WIREs. Comput. Mol. Sci., **11** (2021)*
*[3] D. Silva, D. Weiss, F. Pardo Avila, L. Da, M. Levitt, D. Wang, X. Huang, Proc. Natl. Acad. Sci. U.S.A., **111**, 7665 (2014)*
*[4] A. Golosov, J. Warren, L. Beese, M. Karplus, Structure, **18**, 83 (2010)*
*[5] L. Bonati, G. Piccini, M. Parrinello, Proc. Natl. Acad. Sci. U.S.A., **118** (2021)*
*[6] M. Invernizzi, M. Parrinello, J. Phys. Chem. Lett., **11**, 2731 (2020)*
*[7] L. Bonati, V. Rizzi, M. Parrinello, J. Phys. Chem. Lett., **11**, 2998 (2020)*

Mutational study of the tryptophan tetrad important for electron transfer in European robin cryptochrome 4a

Anders Frederiksen, Ilia A. Solov'yov
University of Oldenburg, Germany

Each year approximately one fifth of the world's known bird species embark on long-distance migration journeys utilizing the geomagnetic field of the Earth along with several other cues to find their way. Despite decades of research and a clear demonstration of the characteristics the understanding of the underlying magnetic navigational mechanism is still elusive. Currently, the strongest magnetoreceptor candidate in birds is a protein called cryptochrome 4a, which is ubiquitously found in bird species. The cryptochrome 4a protein has changed through evolution endowing some birds with a more pronounced magnetic sensitivity than other. Through state-of-the-art molecular dynamics simulations and associated analyses, we have revealed the role of these specific residues in the overall dynamics of the protein. The analyses were further supported through a study of single residue mutations that were used to judge in how far a local change in the protein structure can impact specific dynamics of European robin cryptochrome 4a.

*[1] J. Xu, L. Jarocha, T. Zollitsch, M. Konowalczyk, K. Henbest, S. Richert, M. Golesworthy, J. Schmidt, V. Déjean, D. Sowood, M. Bassetto, J. Luo, J. Walton, J. Fleming, Y. Wei, T. Pitcher, G. Moise, M. Herrmann, H. Yin, H. Wu, R. Bartölke, S. Käsehagen, S. Horst, G. Dautaj, P. Murton, A. Gehrckens, Y. Chelliah, J. Takahashi, K. Koch, S. Weber, I. Solov'yov, C. Xie, S. Mackenzie, C. Timmel, H. Mouritsen, P. Hore, Nature, **594**, 535 (2021)*

Polarizable embedding potentials through molecular fractionation with conjugate caps including hydrogen bonds

David Carrasco de Busturia
Technical University of Denmark, Denmark

Polarizable embedding (PE) is an advanced fragment-based classical embedding model similar to quantum mechanics/molecular mechanics (QM/MM) [1,2]. Unlike mechanical or electrostatic embedding, in PE the polarization between the quantum and classical regions is reciprocal. The quality of the embedding potential is key to provide accurate results for both spectroscopic properties and

dynamical processes. Typically, the embedding potential is derived from the fragmentation of the classical region into smaller fragments. From each individual fragment, the potential parameters, i.e., multipoles and polarizabilities, are derived based on ab-initio calculations. For solvents and other small molecules, the fragments consist of the individual molecules, while for larger molecules (e.g., proteins) further fragmentation is needed. One of the most essential key elements for an accurate embedding potential is a sufficiently robust fragmentation scheme. One such fragmentation strategy is the molecular fractionation with conjugate caps (MFCC) [3], which is used in the PE model. As is widely known, hydrogen bonds play a key role in many biomolecular systems, e.g., in proteins where they are responsible for the secondary structure. In this work, we assess the effects from including hydrogen-bond fragmentation in the MFCC procedure (MFCC-HB) for deriving the multipoles and polarizabilities. It is implemented in PyFraME [4], which is a Python package that automatizes the generation of embedding potentials. The MFCC-HB extension is evaluated on several molecular systems, ranging from small model systems to complex proteins, both directly in terms of electrostatic potentials and indirectly in terms of selected spectroscopic properties of chromophores embedded in protein environments. This implementation will also improve the embedding potential of the related quantum-classical polarizable density embedding (PDE) model.

*[1] N. List, J. Olsen, J. Kongsted, Phys. Chem. Chem. Phys., **18**, 20234 (2016)*
*[2] C. Steinmann, P. Reinholdt, M. Nørby, J. Kongsted, J. Olsen, Int. J. Quantum. Chem., **119**, e25717 (2018)*
*[3] D. Zhang, J. Zhang, The Journal of Chemical Physics, **119**, 3599 (2003)*
[4] J. M. H. Olsen, P. Reinholdt, and contributors, "PyFraME: Python framework for Fragment-based Multiscale Embedding (version 0.4.0)," (2021)

Role of acidic amino acid residues in sequence-specific DNA-protein (SSDP) interactions

Subrahmanyam Sappati, Jacek Czub, Kazi A Hossain, Joanna Slabonskaa
Gdańsk University of Technology, Poland

How a specific DNA-binding protein finds its target substrate-DNA sequence and discriminates all the off-target sequences is an intriguing question, and essential for the understanding of several biological phenomena. Aside from the kinetic aspects, a DNA-binding protein must follow a certain pattern like compact binding to the target site, and loose binding to off-target sites. Therefore, noncovalent interactions such as hydrogen bonding, electrostatic interactions, and hydrophobic interactions (*viz*, VdW) play an important role in sequence-specific DNA-protein interactions. It is well established that the majority of the sequence-specific DNA-protein interactions occur in the major groove of DNA as the functional group of DNA bases are easily accessible for direct interactions/readout (mainly *via* H-bonds) with the amino acid motif of a partner protein. One way to decipher this direct readout is through base-amino acid preference. Hence, we gathered interfacial interaction information of all the DNA/protein complexes from the PDB database. In a previous study from our group on the telomeric repeat-binding factor 1 protein, the role of a specific *Asp* residue in the recognition of the human telomeric sequence containing three consecutive cytosines has been explored by per-residue decomposition of the binding free energy [1]. Interestingly, in this current study, we found that both acidic residues, *Asp* and *Glu*, are quite frequently present at the negatively charged DNA-protein interface, they interact unfavorably with the DNA backbone and thereby may be expected to destabilize the complex. Further analyses suggest that acidic residues can take part in the direct readout *via* interacting with the amino group of cytosine. At the same time, this observation raises the question, of why acidic residue prefers only cytosine and not adenine, even though adenine also has an amino group available for forming H-bond in the major groove? *Asp/Glu* lower the affinity for non-cytosine sites and thus act as negative selectors preventing off-target binding. At cytosine-containing sites, the favorable contribution does not merely rely on the formation of a single H-bond but requires the presence of positive potential generated by multiple cytosines, consistently with the observed excess of cytosine in the target sites. Finally, we show that the preference of Asp/Glu for cytosine over adenine is a result of the repulsion from the adenine imidazole ring and the tendency of purine-purine dinucleotides to adopt the BII conformation. Our results show that acidic residue is mainly involved in the discrimination of off-target sites; sensing the absence of cytosine, Asp/Glu decreases the binding affinity for off-target sites. Finally, using the multiscale modeling (viz, QM, QM/MM) we explain the preference of acidic residues toward cytosine over adenine.

*[1] M. Wieczór, J. Czub, Nucleic Acids Research, **45**, 7643 (2017)*

Spectroscopic properties using polarizable embedding: going beyond the cutoff schemes with the minimum image convention

Sonata Kvedaraviciute
Technical University of Denmark, Denmark

The simulation of spectroscopic processes using quantum chemistry methods plays an increasingly important role in fundamental research where it establishes the bridge between theory and experiment. However, their application is limited to small molecular systems due to the unfavorable scaling of the computational cost with system size. Fortunately, many spectroscopic processes are spatially localized and therefore only a relatively small part needs a quantum mechanical (QM) description. Still, the environment surrounding the central part plays a crucial role. To model realistic systems, one, therefore, needs to have an accurate and computationally efficient description of the environment. For this, we use the polarizable embedding (PE) model which is an advanced QM/MM-type scheme that includes mutual polarization between the quantum and classical parts through induced dipoles [1,2]. Typical applications using the PE model are based on a cutoff-based approach where a small part of the entire system is cut out and used in the calculations. This results in an unphysical description of the induced electrostatics, in particular at the outer edges of the environment, and also adds a dependence on the cutoff distance.
In this work, a periodic boundary treatment via the minimum image convention (MIC) is introduced for the induced electrostatics (*PE-MIC*) and implemented in the Dalton program [3]. This enables a more physically accurate description of environment effects since all polarizable sites are always surrounded by the entire system. It is compared to the standard cutoff-based approach in terms of modeling excitation energies and associated oscillator strengths and two-photon absorption cross-sections.
First, we investigate the performance for solute-solvent systems, namely 4-nitrophenolate (PNP1), 4'-nitro-4-biphenylate (PNP2), and 4-[(E)-2-(4-nitrophenyl)-vinyl]phenolate (PNP3) dissolved in water [4]. Then, we focus on the Nile red chromophore in heterogeneous biomolecular environments, i.e., embedded in a beta-globuline protein [5] and in a phosphatidylcholine membrane [6].
The results using the standard cutoff-based PE scheme show that the investigated spectroscopic properties are sensitive to the cutoff and do not always converge at typical cutoff distances, i.e., 12-14 Å for solute-solvent systems. Moreover, they do not always converge to the value produced by *PE-MIC* which shows that the unphysical description of the induced electrostatics at the system boundaries has an effect even at large distances from the quantum part.

*[1] C. Steinmann, P. Reinholdt, M. Nørby, J. Kongsted, J. Olsen, Int. J. Quantum. Chem., **119**, e25717 (2018)*
*[2] J. Olsen, K. Aidas, J. Kongsted, J. Chem. Theory Comput., **6**, 3721 (2010)*
*[3] K. Aidas, C. Angeli, K. Bak, V. Bakken, R. Bast, L. Boman, O. Christiansen, R. Cimiraglia, S. Coriani, P. Dahle, E. Dalskov, U. Ekström, T. Enevoldsen, J. Eriksen, P. Ettenhuber, B. Fernández, L. Ferrighi, H. Fliegl, L. Frediani, K. Hald, A. Halkier, C. Hättig, H. Heiberg, T. Helgaker, A. Hennum, H. Hettema, E. Hjertenaes, S. Høst, I. Høyvik, M. Iozzi, B. Jansík, H. Jensen, D. Jonsson, P. Jørgensen, J. Kauczor, S. Kirpekar, T. Kjaergaard, W. Klopper, S. Knecht, R. Kobayashi, H. Koch, J. Kongsted, A. Krapp, K. Kristensen, A. Ligabue, O. Lutnaes, J. Melo, K. Mikkelsen, R. Myhre, C. Neiss, C. Nielsen, P. Norman, J. Olsen, J. Olsen, A. Osted, M. Packer, F. Pawlowski, T. Pedersen, P. Provasi, S. Reine, Z. Rinkevicius, T. Ruden, K. Ruud, V. Rybkin, P. Sałek, C. Samson, A. de Merás, T. Saue, S. Sauer, B. Schimmelpfennig, K. Sneskov, A. Steindal, K. Sylvester-Hvid, P. Taylor, A. Teale, E. Tellgren, D. Tew, A. Thorvaldsen, L. Thøgersen, O. Vahtras, M. Watson, D. Wilson, M. Ziolkowski, H. Ågren, WIREs. Comput. Mol. Sci., **4**, 269 (2013)*
*[4] E. Kjellgren, J. Haugaard Olsen, J. Kongsted, J. Chem. Theory Comput., **14**, 4309 (2018)*
[5] P. Hartmann, P. Reinholdt, J. Kongsted, Polarizable Embedding as a Tool to Address Light-Responsive Biological Systems (2020)
*[6] S. Prioli, P. Reinholdt, M. Hornum, J. Kongsted, J. Phys. Chem. B, **123**, 10424 (2019)*

Structural and dynamic properties of poly(ethylene oxide)/silica nanocomposites as studied by molecular dynamics simulations

Ioannis Tanis, Vangelis Harmandaris
The Cyprus Institute, Cyprus

Polymer nanocomposites (PNCs) prepared by introducing nanoparticles (NPs) (spheres, cylinders, plates) within a polymer matrix, have attracted significant scientific and technological interest since the addition of a small volume of nanofillers creates a great amount of interfacial area between polymer matrix and nanofillers, resulting in either improved or new properties without losing attractive properties inherent to pure polymers such as toughness, processability and optical transparency. Molecular dynamics simulation is a complementary tool to experiments as it offers a detailed and direct insight

into the properties of a polymer matrix embedded with spherical NPs. Motivated by pertinent experimental and numerical works, we examine structural and dynamic attributes of a poly(ethylene oxide)/silica PNC in a wide range of temperatures sampling both the melt and the glassy state. The effect of NP concentration is also addressed. Our results demonstrate that the dynamics of the adsorbed chains is slower compared to their non-adsorbed counterparts and indicate a coupling between the chain conformational states and their segmental dynamics.

Tau protein binding modes in alzheimer's disease for cationic luminescent ligands

Yogesh Todarwal[1], Camilla Gustafsson[1], Nghia Nguyen Thi Minh[2], Ingrid Ertzgaard[3], Therése Klingstedt[4], Bernardino Ghetti[5], Ruben Vidal[5], Carolin König[2], Mikael Lindgren[3], K. Peter R. Nilsson[4], Mathieu Linares[4]
[1]KTH Royal Institute of Technology, Sweden
[2]Leibniz University Hannover, Germany
[3]Norwegian University of Science and Technology, Trondheim, Norway
[4]Linköping University, Sweden
[5]Indiana University School of Medicine, United States

The bi-thiophene-vinylene-benzothiazole (bTVBT4) ligand developed for Alzheimer's disease (AD)-specific detection of amyloid tau has been studied by a combination of several theoretical methods and experimental spectroscopies. With reference to the cryo-EM tau structure of the tau protofilament [1], a periodic model system of the fibril was created, and the interactions between this fibril and bTVBT4 were studied with nonbiased molecular dynamics simulations. Several binding sites and binding modes were identified and analyzed, and the results for the most prevailing fibril site and ligand modes are presented. A key validation of the simulation work is provided by the favorable comparison of the theoretical and experimental absorption spectra of bTVBT4 in solution and bound to the protein. It is conclusively shown that the ligand–protein binding occurs at the hydrophobic pocket defined by the residues Ile360, Thr361, and His362. This binding site is not accessible in the Pick's disease (PiD) fold, and fluorescence imaging of bTVBT4-stained brain tissue samples from patients diagnosed with AD and PiD provides strong support for the proposed tau binding site.

[1] A. Fitzpatrick, B. Falcon, S. He, A. Murzin, G. Murshudov, H. Garringer, R. Crowther, B. Ghetti, M. Goedert, S. Scheres, Nature, ***547****, 185 (2017)*
[2] H. Shirani, H. Appelqvist, M. Bäck, T. Klingstedt, N. Cairns, K. Nilsson, Chem. Eur. J., ***23****, 17127 (2017)*
[3] C. König, R. Skånberg, I. Hotz, A. Ynnerman, P. Norman, M. Linares, Chem. Commun., ***54****, 3030 (2018)*

Towards an understanding of Turbo-Grignard reagents: structural information from AIMD studies

Marinella de Giovanetti[1], Odile Eisenstein[2], Michele Cascella[1]
[1]University of Oslo, Norway
[2]ICGM, University of Montpellier, France

Alkali and alkaline-earth organometallic reagents constitute today a critical asset for the synthesis of a broad range of valuable compounds, and are used daily in academy and industry. In recent years, bimetallic formulations resulting from the association of main-group organometallic reactants with LiCl, so-called Turbo reagents, have attracted great attention in light of the boosted properties they offer to such a critical class of compounds. The powerfulness of such association can be illustrated by the remarkable improvements offered t o one of the most prominent functionalization tools in organic synthesis, Grignard reagents (RMgCl). Compared to pure Grignard reactants, the metallation promoted by Turbo-Grignards (RMgCl·LiCl) proceeds selectively, with high-group tolerance and in high-yields (1). The enhancement provided by the association with LiCl awarded iPrMgCl·LiCl the Encyclopedia of Reagents for Organic Chemistry (EROS) best reagent award in 2011. Despite the success of these bimetallic formulations, the current understanding of the origin of the beneficial association with LiCl remains rather unsatisfactory, so far attributed to unidentified synergistic effects between the two metals. In our group, we recently used ab initio molecular dynamics (AIMD) coupled to enhanced sampling techniques to determine the mechanism of the Grignard reaction at its molecular level in THF (2). Here, we used the same approach to characterize the structure of LiCl in solution and its interaction

with Grignard reagents. AIMD simulations revealed that the symmetric crystallographic $(LiCl)_4(THF)_4$ structure observed when crystallizing the compound at low temperature is not representative of the molecular moiety present in liquid THF at room conditions. This is instead a very dynamic, non-symmetrical species, where key is the role of the solvent, in agreement with our previous findings for Grignard reagents (3). In particular, $(LiCl)_4$ takes the form of a distorted cube where one of the twelve Li-Cl bonds is broken, in favor of the coordination of an additional THF molecule at the Li site. The intrinsic weakening of a Li-Cl interaction promotes the aggregation of the $(LiCl)_4$ cluster with the Grignard species through the formation of a Li-Cl-Mg-Cl wire. The binding affinity between $(LiCl)_4$ and RMgCl can control the distribution of the species present in solution by disturbing the Schlenk equilibrium.

*[1] S. Robertson, M. Uzelac, R. Mulvey, Chem. Rev., **119**, 8332 (2019)*
*[2] R. Peltzer, J. Gauss, O. Eisenstein, M. Cascella, J. Am. Chem. Soc., **142**, 2984 (2020)*
*[3] R. Peltzer, O. Eisenstein, A. Nova, M. Cascella, J. Phys. Chem. B, **121**, 4226 (2017)*

Towards proton transfer regulated self-activation of oxidized nDsbD

Aparna Gopalakrishnan Nair[1], D. Sravanakumar Perumalla[2], Padmesh Anjukandy[1]
[1]Indian Institute of Technology Palakkad, India
[2]Linköping University, Sweden

Proton transfer reaction is fundamental to many biological processes, including enzyme catalysis and cell signaling. Certain enzymes can reversibly alter the redox states of catalytic disulfide bonds with nucleophiles generated by proton transfer.[1] Considering the readiness of the disulfide bond towards nucleophilic cleavage, it is also plausible that an internal nucleophile could second the existing electron transfer mechanism (termed “Self-activation”) in the oxidized N-terminal Disulfide bond oxidoreductase ($nDsbD_{Ox}$), the redox hub in gram-negative bacteria.[2]
Here, we explored the possibility of internal nucleophile formation ($Tyr_{42}O^-$) in the active site of the protein and followed by the disulfide cleavage in $nDsbD_{Ox}$ to form reduced $nDsbD_{Red}$ The proton transfer assisted formation of $Tyr_{42}O^-$ (from Tyr_{42} and Asp_{68})[3] in $nDsbD_{Ox}$ is studied using QM/MM molecular dynamics clubbed with multiple-walker metadynamics technique. The results confirm the formation of the internal nucleophile $Tyr_{42}O^-$ ($\Delta F \sim 9$ kcal/mol) and its stabilization through the solvent medium. In addition, it is identified that OH^- is also formed by the proton transfer from water to $Tyr_{42}O^-$but remains in the proximity of $Tyr_{42}O^-$ and is incapable of diffusing away from the reaction site. The gas-phase static calculation provides promising results of $Tyr_{42}O^-$ mediated α-elimination (abstraction of a proton from $Cys_{103}C_\alpha$, barrier height ~ 10.98 kcal/mol) in achieving disulfide scission and thus the self-activation of $nDsbD_{Ox}$. Further, it is also observed that the formation of the internal nucleophile in $nDsbD_{Ox}$ is regulated by a water network involved in proton communication between $Tyr_{42}O^-$ and $Asp_{68}OH$ residues ($\Delta F\sim$ 12 kcal/mol).[4] Our analysis suggests the proton transport through proton-hole (OH^- propagation) rather than the common Grotthuss mechanism (H_3O^+ propagation). Thus, for the first time, we demonstrate the generation of the internal nucleophile ($Tyr_{42}O^-$), followed by the role of solvent in proton-hole-assisted nucleophile regulation, near the active site $nDsbD_{Ox}$. We believe that the internal nucleophilic reaction channel would be helpful when designing novel nDsbD inhibitors.

*[1] R. P. Neves, P. A. Fernandes and M. J. Ramos, Proc. Natl. Acad. Sci. **114,** E4724 (2017)*
*[2] F. Katzen, J. Beckwith, Cell, **103**, 769 (2000)*
*[3] C. Goulding, M. Sawaya, A. Parseghian, V. Lim, D. Eisenberg, D. Missiakas, Biochemistry, **41**, 6920 (2002)*
*[4] A. Nair, D. Perumalla, P. Anjukandi, Phys. Chem. Chem. Phys., **24**, 7691 (2022)*

5. Participant list

Organizers

Meloni, Simone
University of Ferrara, Italy
Olsen, Jógvan Magnus Haugaard
Technical University of Denmark, Denmark
Roethlisberger, Ursula
EPFL, Switzerland

On-site participants

Agosta, Lorenzo - EPFL, Switzerland
Ahmadzadeh, Karan - KTH, Sweden
Antalík, Andrej - EPFL, Switzerland
Carloni, Paolo - Forschungszentrum Jülich & RWTH Aachen University, Germany
Carrasco De Busturia, David - Technical University of Denmark, Denmark
De Giovanetti, Marinella - University of Oslo, Norway
Duerr, Simon - EPFL, Switzerland
Figueroa, David - Italian Institute of Technology, Italy
Frederiksen, Anders - University of Oldenburg, Germany
Gopalakrishnan Nair, Aparna - Indian Institute of Technology Palakkad, India
Goullieux, Mathilde - SIB, Switzerland
Hagemann, Marlisa M. - University of Southern Denmark (SDU), Denmark
Johnson, Sophia - EPFL, Switzerland
Kvedaraviciute, Sonata - Technical University of Denmark, Denmark
Levy, Andrea - EPFL, Switzerland
Malapally, Nitin - Forschungszentrum Juelich, Germany
Mandelli, Davide - FZJ, Germany
Mbah Chrameh, Fru - University of Stockholm, Sweden
Ntarakas, Nikolaos - National Institute of Chemistry, Slovenia
Palermo, Giulia - University of California Riverside, United States
Parise, Angela - Scuola Internazionale Superiore di Studi Avanzati - SISSA, Italy
Persson, Louise - Uppsala University, Sweden
Raghavan, Bharath - Forschungszentrum Juelich, Germany
Sappati, Subrahmanyam - Gdańsk University of Technology, Poland
Schackert, Florian - Forschungszentrum Jülich, Germany
Tanis, Ioannis - The Cyprus Institute, Cyprus
Todarwal, Yogesh - KTH Royal Institute of Technology, Sweden
Visigalli, Alessia - Istituto Italiano di Tecnologia, Italy

On-line participants

Ahsan, Mohd - University of California Riverside, United States
Banerjee, Debarshi - ICTP - International Centre for Theoretical Physics, Italy
Bishnoi, Bhupesh - National Institute of Advanced Industrial Science and Technology, Japan
Bonilla, Mauricio - Basque Center for Applied Mathematics, Spain
Chanana, Anuja - JNCASR, India
De Nicola, Antonio - University of Salerno, Italy
Dey, Aditya - University of Rochester, United States
Firmino, Vinicius - University of São Paulo, Brazil

Gladkikh, Vladislav - Institute for Basic Science, Republic of Korea
Ishrat, Jahan - Indian Institute of Technology Delhi, India
Jena, Nityasagar - Université de Mons, Belgium
Mahabal, Manasi - S. P. Pune University, India
Mohamed, Ibrahim - Faculty of Science, Cairo University, Egypt
Nair, Anoop A - University of Iceland, Iceland
Nosratjoo, Mohamadhosein - University of Tehran, Iran
Oyebamiji, Abel Kolawole - Adeleke University, Nigeria
Rajamani, Akilan - University of Lille, France
Roy, Projesh Kumar - The Institute of Mathematical Sciences, Chennai, India
Saha, Aakash Saha - University of California, Riverside, United States
Singh, Pragyansh - Indian Institute of Technology Madras, India
Vidossich, Pietro - Istituto Italiano di Tecnologia, Italy