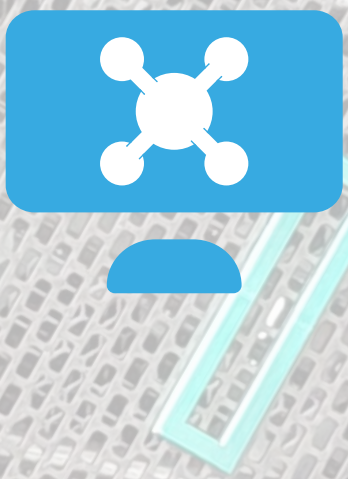
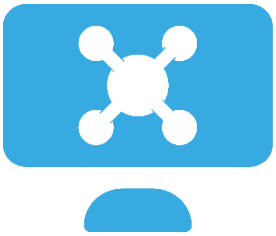


COMPUTATIONAL CHEMISTRY DAY 2023

Book of abstracts

Department of Chemistry
University of Zagreb Faculty of Science

September 15th–16th, 2023
Zagreb, Croatia, EU



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Foreword

This is our fourth conference in a row (with the exception of two Covid years). In a sense we have made a full circle, getting back to the first conference site - the Department of Chemistry, Faculty of Science. We are happy to keep continuity (as much as it was possible) and free access to the conference. Despite permanently looking for new speakers, we are inevitably running out of them because of the finite size of our community and, more importantly, because the rejuvenation process seems to be slowing down. On the other hand, we are attempting to grow into an international conference and to attract participants, especially speakers, from abroad as well. This year we luckily succeeded, thanks to the collaboration of our colleagues with some European universities. We hope to continue this trend in the future! This year the conference is for the first time extended by a workshop, something that we wished for from the beginning. Those willing to share their knowledge and experience are cordially invited to join us. We will keep including the practical value contents, for example, this year, in the contributed lecture on the computational chemistry software installed on Supek and some characteristics of its use.

The greatest event in the last year was the launching of the supercomputer Supek at the University Computing Centre Srce, University of Zagreb. This is a strong impetus to all Croatian researchers using advanced computing resources, with computational chemistry being among the most prominent. The University Computing Centre Srce has done a brilliant job as the leader of the project HR-ZOO, which included not only building the supercomputer but also the advanced data storage capacities located at the universities of Osijek, Rijeka, Split and Zagreb, as well as the fast and reliable communication between them. The project cost was more than 26 million EUR, with 85% provided by the European Regional Development Fund. Realization of this project is a necessary step for keeping Croatian science and education competitive on the global scene.

Some of us expected that Supek would be soon fully engaged and populated by users as it was the older (and much smaller) computational cluster Isabella. However, it hasn't happened yet, even after almost half a year from opening. Summer holidays are certainly a part of the reason for that, and the half-empty Isabella cluster at the same time confirms this. On the other hand, the relatively strict and unprecedented procedure for getting access to Supek, based on the ongoing project plainly registered in CroRIS, is an obstacle that many scientists have to resolve. This is also related to a diminishing number of HrZZ projects which not only provide a conceptual framework for research activities, but also financial support for the PhD and postdoctoral students who constitute the major part of active users.

Next year, we do not plan another conference in this series because it would overlap with the next Central European Symposium on Theoretical Chemistry that will take place in Croatia, in St. Martin on Muir, September 11–14 (locally organized by Nađa Došlić and Tomica Hrenar). All of you are invited to take this opportunity and meet scientists in theoretical chemistry (and computational as well) at this bigger event. In 2025, we plan to get back into the initial timeframe in spring.

We wish you good luck and success in your computational endeavors.

The Organizing Committee

Program of the *Computational Chemistry Day 2023*

Pre-conference workshop

Friday, September 15th, 2023 (Location: Department of Chemistry, Faculty of Science, Horvatovac 102a, P2 lecture hall)

16:00 – 19:00 Emir Imamagić (Srce, Zagreb) and Davor Šakić (FPB, Zagreb)
Introductory and Advanced Use of Scripting in Computational Chemistry

The Conference

Saturday, September 16th, 2023 (Location: Department of Chemistry, Faculty of Science, Horvatovac 102a, A1 lecture hall).

08:45 – 09:00 **Opening addresses**

1st session (moderator: Darko Babić)

09:00 – 09:30 **Marin Sapunar (RBI, Zagreb)**
Determining neutral fragments formed by electron impact excitation of large molecules (IL)

09:30 – 10:00 **Vedran Miletić and Matea Turalija (FIDT, Rijeka)**
Molecular dynamics simulation for exascale supercomputing era: scientific research and software engineering challenges (IL)

10:00 – 10:15 **Gordan Horvat (DC-FS, Zagreb)**
On the interface between experiment and computation, the experimentalist's viewpoint (CL)

10:15 – 10:30 **Gaëlle Bouder (UPPA, Pau, France) and Philippe Carbonniere**
Degradation of the interface between fluorinated polymer electrolyte and lithium metal anode using first-principles theory (CL)

10:30 – 11:00 **Coffee break**

2nd session (moderator: Robert Vianello)

11:00 – 11:30 **Ivan Kodrin (DC-FS, Zagreb), Ivana Biljan, Marijana Đaković and Mojca Čakić Semenčic**
Computational chemistry as a tool for the design of functional materials (IL)

11:30 – 12:00 **Višnja Stepanić (RBI, Zagreb), Zlatko Brkljača and Maja Majerić Elenkov**
Computational insights into the biocatalytic activity of C-type halohydrin dehalogenase HheC (IL)

12:00 – 12:15 **Giovana Miti Aibara Paschoal (UPPA, Pau, France), William Lafargue-Dit-Hauret, Roger C. Hiorns and Didier Bégué**

Molecular design and computational investigation of optoelectronic properties of conjugated polymers for OPV cells (CL)

12:15 – 12:30 **Luis Acevedo (UPPA, Pau, France), Jimmy Castillo and Germain Salvato Vallverdu**
Aggregation phenomenon and effects of trapped compounds in complex mixture by molecular dynamics simulations (CL)

12:30 – 12:45 **Emir Imamagić (Srce), Kristijan Mrkalj (Srce), Tomica Hrenar, Darko Babić and Borislav Kovačević**
Computational chemistry on the Supek supercomputer (CL)

12:45 – 14:30 **Lunch break (level 0)**

3rd session (moderator: Ivan Kodrin)

14:30 – 15:00 **Zoran Štefanić (RBI, Zagreb), Aleksandra Maršavelski and Boris Gomaz**
Allosteric communication in enzymes through advanced visualization of MD simulations (IL)

15:00 – 15:30 **Karlo Sović (DC-FS, Zagreb)**
Modelling multidimensional potential energy surfaces by deep reinforcement learning (IL)

15:30 – 16:00 **Marina Juribašić (RBI, Zagreb)**
Computational study of deuteration of palladated azobenzenes by cysteine-d4 (IL)

16:00 – 16:15 **Željka Sanader Maršić (FS, Split), Dušica Maysinger, Evan Rizzel Gran, Adeola Shobo, Jun-Ray Macairan, Issan Zhang, Martina Perić Bakulić, Rodolphe Antoine, Gerhard Multhaup and Vlasta Bonačić-Koutecky**
Insights into the impact of gold nanoclusters Au10SG10 on human microglia (CL)

16:15 – 16:30 **Marina Šekutor (RBI, Zagreb)**
Characterization of diamondoid clusters emerging in helium nanodroplets (CL)

16:30 – 16:45 **Bruno Mladineo (RBI, Zagreb)**
A machine learning approach to study of thermosalient molecular crystals (CL)

16:45 – 16:50 **Concluding remarks**

Poster and e-poster session with more coffee (levels 0 and -1)

17:15 – 17:30 **Online polls for the best poster and the best e-poster**

17:30 – 17:45 **The best poster and the best e-poster awards**

(IL): invited lecture, (CL): contributed lecture

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Lectures

IL 1. Determining Neutral Fragments Formed by Electron Impact Excitation of Large Molecules

Marin Sapunar[a,b,c]

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Electronic excitation of molecules through electron impact is one of the key processes governing the chemistry in systems where electron collisions can occur. However, the neutral fragments commonly formed after such excitations are more difficult to detect than the ions formed by competing processes such as dissociative attachment or ionization and accurate theoretical models are usually difficult to apply and limited to small systems.

A recent implementation of the Born approximation in the UKRMol+ suite [1] is presented. This approximation describes the scattering electron only in the most basic terms possible, but in return can be combined with descriptions of the wave functions of the target molecule much more advanced than would be possible in standard scattering calculations. This advantage is used to study industrially important molecules too large for other types of simulations.

In the first study [2], the excited state chemistry of heptafluoroisobutyronitrile (a candidate for the replacement of sulphur hexafluoride for use as an insulating medium) is explored through a combination of theory and experiments. In the second (preliminary) study, the possibility of degradation of a series of perfluoroalkyl substances (PFAS) using plasma is evaluated.

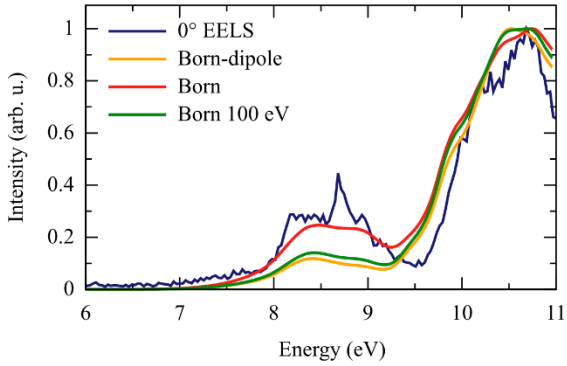

Figure 1. Forward direction electron energy loss spectrum (experimental and simulated) of the dielectric gas C_4F_7N showing the dependence of the spectrum on the incoming energy of the electrons [2].

References:

[1] Z. Mašín, J. Benda, J. D. Gorfinkiel, A. G. Harvey, J. Tennyson, *Comput. Phys. Commun.*, **249** (2020) 107092.

[2] T. Ovad, M. Sapunar, Š. Sršeň, P. Slavíček, Z. Mašín, N. C. Jones, S. V. Hoffmann, M. Ranković, J. Fedor, *J. Chem. Phys.* **158** (2023) 014303.

IL 2. Molecular Dynamics Simulation for Exascale Supercomputing Era: Scientific Research and Software Engineering Challenges

Vedran Miletić and Matea Turalija

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Group for Applications and Services on Exascale Research Infrastructure, Faculty of Informatics and Digital Technologies, University of Rijeka, Radmile Matejčić 2, 51000 Rijeka, Croatia

The new era in supercomputers started last year with the arrival of the first batch of exascale supercomputers to the TOP500 list. Compared to the previous-generation petascale supercomputers, such computers require the use of much more complex software models and algorithms to make optimal use of all available computing resources. In the last ten years, several partnerships and projects have been launched to develop and adapt software for the "exascale era", examples of which are the German Software for Exascale Computing (SPPEXA), the American Exascale Computing Project (ECP), the European High-Performance Computing Joint Undertaking (EuropHPC JU), and Croatian High performance scalable algorithms for future heterogeneous distributed computing systems (HybridScale).

Specifically, in the SPPEXA programme [1], progress has been made with adapting many software packages for the expected exascale supercomputer architectures, including the popular open-source molecular dynamics (MD) simulation software GROMACS [2]. The present approach is focused on developing and implementing the fast multipole method (FMM) in place of particle mesh Ewald (PME). Our group has joined this effort in collaboration with Max Planck Institute for Multidisciplinary Sciences (MPI-NAT) in Goettingen, Germany with the goals of expanding the range of supported simulation box shapes and extending the accelerator support to smart network interface cards, also known as data processing units.

The talk will cover the architectural changes of exascale supercomputers and their impact on scientific software development. The specific focus will be on potential for further development of the molecular dynamics simulation algorithms in GROMACS and the expected impact of these developments on the larger ecosystem of computational biochemistry tools.

References:

[1] SPPEXA. http://www.sppexa.de

[2] GROMACS. https://www.gromacs.org

IL 3. Computational Chemistry as a Tool for the Prediction of Functional Materials

Ivan Kodrin,[a] Ivana Biljan,[a] Marijana Đaković[a] and Mojca Čakić Semenčić[b]

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[b]*Department of Chemistry and Biochemistry, Faculty of Food Technology and Biotechnology, University of Zagreb, Pierottijeva 6, 10000 Zagreb, Croatia*

Computational chemistry combines numerical methods based on quantum chemistry (QC), molecular mechanics (MM), molecular dynamics (MD) and Monte Carlo (MC) simulations for the prediction of the structure, electronic and thermodynamic properties of chemical systems. Nowadays, computational chemistry gives the opportunity to predict the properties of new functional materials relatively accurately and rapidly in a more cost-effective way than is possible experimentally. In this overview, an outline of the current computational chemistry approaches for a better understanding of diverse chemical systems and for the design of new functional materials is highlighted. The current procedures rely on MM conformational analysis and QM calculations (population analysis, simulation of circular dichroism spectra) calculations of simple ferrocene peptidomimetics in order to understand the transfer of chiral information in chiroptical sensors with ferrocene chromophores [1]. The development of new systems, like porous organic polymers, capable of sequestering CO_2 from the atmosphere or capturing that emitted from human activities is one of the major challenges in science today. Periodic DFT calculations allow us to easily model different topologies of covalent organic frameworks made of various building blocks connected by nitrogen-nitrogen linkages such as azo, azoxy and azodioxy [2]. Electrostatic potential values (ESP) can even help us to predict the CO_2 adsorption properties of such systems and the most favourable binding sites between the framework and gas molecules which can be further evaluated by grand-canonical Monte Carlo simulations. The importance of computational analysis of intermolecular interactions is nicely demonstrated in the study of two-dimensional anisotropic flexibility of mechanically responsive crystalline coordination polymers [3]. In combination with experimental findings, the role of computational chemistry is to give deeper knowledge about the chemical systems at the molecular level and hopefully provide a better understanding of structure-property relationships.

References:

[1] M. Nuskol, P. Šutalo, M. Đaković, M. Kovačević, I. Kodrin, M. Čakić Semenčić, *Organometallics* **40** (2021) 1351–1362.

[2] T. Frey, B. Panić, P. Šutalo, M. Borovina, I. Biljan, I. Kodrin, *CrystEngComm* **25** (2023) 3870–3884.

[3] M. Pisačić, I. Kodrin, A. Trninić, M. Đaković, *Chem. Mater.* **34** (2022) 2439–2448.

IL 4. Computational Insights into the Biocatalytic Activity of C-Type Halohydrin Dehalogenase HheC

Višnja Stepanić,[a] Zlatko Brkljača[a,b] and Maja Majerić Elenkov[a]

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[a]*Ruđer Bošković Institute, Bijenička 54, 10000 Zagreb, Croatia*
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The tetrameric enzyme halohydrin dehalogenase from *Agrobacterium radiobacter* AD1, HheC (Figure 1) is widely explored for industrial production of stereospecific hydroxylated or epoxide precursors for drugs and agrochemicals. In order to expand the chemical substrate space and/or alter stereospecificity, various mutants of this biocatalyst have been prepared and the effects of a range of solvents have been explored. In the presentation, two types of contributions of MD calculations to the interdisciplinary study of optimizing the biocatalytic activity of HheC will be shown: i) understanding the effects of adding DMSO to aqueous solution on the catalytic activity of HheC [1] and ii) explaining the effects of the rationally selected quadrupole mutations on the stereospecificity of HheC [2].

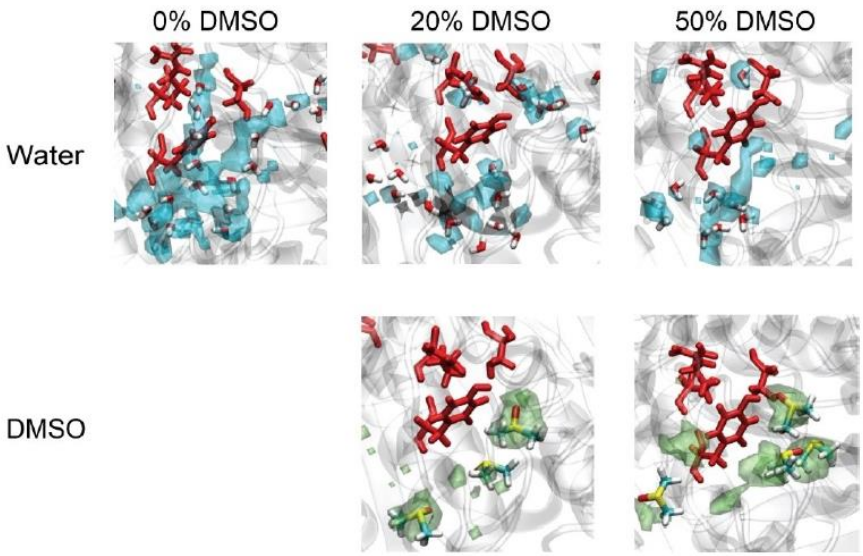

Figure 1. DMSO is a competitive inhibitor of HheC. Volumetric maps of water (blue) and DMSO (green) inside the substrate binding site of HheC, obtained from the last 100 ns of the tetramer simulations for different DMSO/water volume ratios [1].

References:

[1] N. Milčić, V. Stepanić, I. Crnolatac, Z. Findrik Blažević, Z. Brkljača, M. Majerić Elenkov, *Chem. Eur. J.* **28** (2022) e202201923. doi: 10.1002/chem.202201923

[2] I. Dokli, Z. Brkljača, P. Švaco, L. Tang, V. Stepanić, M. Majerić Elenkov, *Org. Biomol. Chem.* **20** (2022) 9734–9741. doi: 10.1039/D2OB01955H

IL 5. Allosteric Communication in Enzymes Through Advanced Visualization of MD Simulations

Zoran Štefanić,[a] Aleksandra Maršavelski[b] and Boris Gomaz[a]

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One way we can try to understand the phenomenon of allostery in proteins is to observe how certain parts of a protein move in correlation with others over time. Since proteins are vey complex molecules, and protein MD simulations have millions of individual steps, we have to find the way to observe a small portion of those connected motions from sea of unrelated motions. The ALOKOMP project [1] is specifically dedicated to understanding the nature of allostery and allosteric communication in one class of enzymes (PNPs) [2]. To handle the extensive data in the database, we leverage programmatic methods and visualization techniques that capture the underlying relationships within the data. Novel time-dependent Ramachandran diagrams (Figure 1) were created to capture the conformational changes of individual amino acids throughout the trajectory.

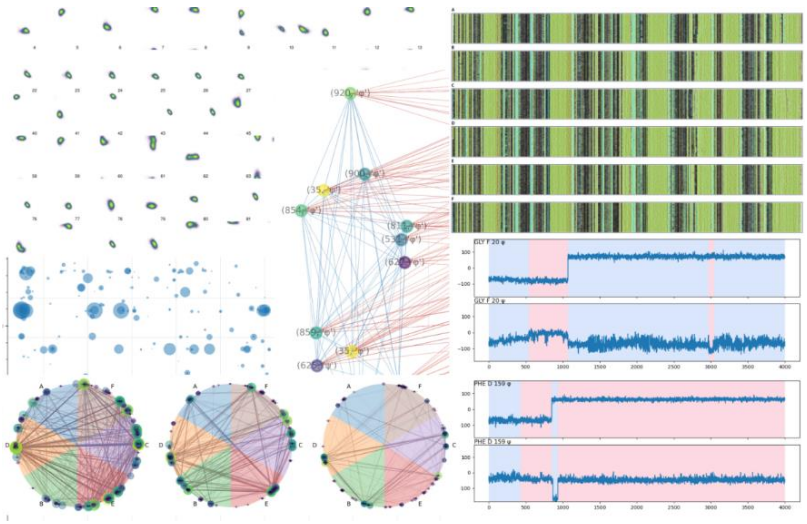

Figure 1. Various visualization tools used to detect allosteric communications in the project ALOKOMP.

By combining these diagrams for all amino acids, a comprehensive depiction of the protein's conformational changes was achieved. Correlation analysis was conducted on the phi and psi angles of the amino acids, revealing correlated and anti-correlated movements within the protein. As expected, a significant portion of the protein exhibited random movement, but also some underlying patterns were observed, indicating possible hubs of allosteric communication. Throughout the study, various Python visualization tools were utilized to analyze and effectively present the obtained data. The research contributes to the understanding of allostery in PNPs and provides valuable insights into the structural dynamics of these enzymes.

References:

[1] This research is part of the ongoing project *Allosteric communication pathways in oligomeric enzymes* (ALOKOMP, https://alokomp.irb.hr, financed by Croatian Science Foundation grant no. IP-2019-04-6764).

[2] M. Narczyk, M. I. Wojtyś, I. Leščić Ašler, B. Žinić, M. Luić, E. K. Jagusztyn-Krynicka, Z. Štefanić, A. Bzowska, *J. Enzyme Inhib. Med. Chem.* **37** (2022) 1083–1097.

IL 6. Modelling Multidimensional Potential Energy Surfaces by Deep Reinforcement Learning

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Department of Chemistry, Faculty of Science, University of Zagreb,
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In modern theoretical chemistry one of the most important challenges is designing and implementing approximations that accelerate computations without loss of accuracy. Some of the strategies include partition of the system of interest into fragments, linear scaling or semi-empirical methods and construction of empirical potentials that have been parameterized to reproduce experimental or accurate calculations. Deep learning (DL) is emerging as a powerful approach to construct various forms of transferable and non-transferable potentials utilizing machine learning (ML) methods and multilayer neural networks (NN) [1]. These methods have been successfully applied in various applications in chemistry, including the prediction of reaction pathways [2], excited state energies [3], formation energies [4], and nuclear magnetic resonance chemical shifts [5].

In this study, deep reinforcement learning, implemented in ***moonee*** [6] program, was used to calculate multilinear models and to train multilayer neural networks for describing PESs of benzene and its heterocyclic analogues spanned by their normal coordinates. All quantum-chemical calculations were performed using Gaussian16 program package at the B3LYP-D3/aug-cc-pVTZ level of theory using ***qcc*** [7] program for generating relevant configurations of investigated systems. A particular strength of multilayer neural networks is that they can fit any real-valued, continuous function of *n*-dimensions to arbitrary accuracy using a finite number of parameters. For all examined PESs, multilayer neural networks have shown that they can reproduce accurate descriptions of investigated PESs using only a smaller number of total data points. Also, the machine learning algorithm calculated the best possible multilinear models for each investigated PES up to the desired degree of a polynomial. The computational cost of performing deep reinforcement learning is reasonably small and we expect that this procedure will be useful in modeling a wide variety of PESs at the high level of theory for further quantum-chemical calculations.

References:

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[2] B. Jiang, J. Li and H. Guo, *Int. Rev. Phys. Chem.* **35** (2016) 479–506.

[3] F. Häse, S. Valleau, E. Pyzer-Knapp, A. Aspuru-Guzik, *Chem. Sci.* **7** (2016) 5139–5147.

[4] F. A. Faber, A. Lindmaa, O. A. von Lilienfeld, R. Armiento, *Phys. Rev. Lett.* **117** (2016) 135502.

[5] M. Rupp, R. Ramakrishnan, O. A. von Lilienfeld, *J. Phys.Chem. Lett.* **6** (2015) 1–5.

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IL 7. Computational Study of Deuteration of Palladated Azobenzenes by Cysteine-d_4

Marina Juribašić Kulcsár, Alen Bjelopetrović, Dajana Barišić, Ivan Halasz, Manda Ćurić and Stipe Lukin

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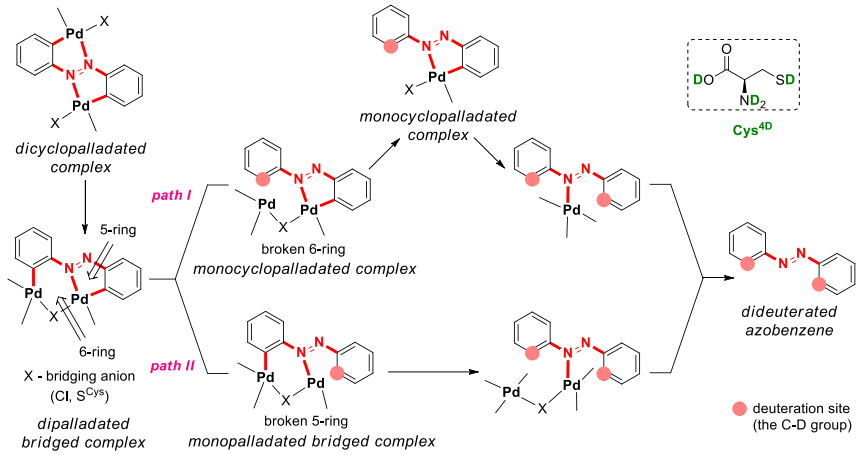
Development of methods for direct and selective deuteration remains a challenge for the chemical and life sciences, as D-labeled compounds are widely used in mass spectrometry and chromatography, medicinal chemistry, and mechanistic and metabolic studies [1].

Recently, we used palladated products with Pd-activated C–H bond(s) as precursors for solid-state deuteration, using a deuterated L-cysteine (**Cys^{4D}**, Scheme 1) as the D-source [2]. This work showed that **Cys^{4D}** can break the C–Pd bond and transfer a deuteron to the carbon atom. Using this simple strategy, various deuterated organic molecules were isolated and their formation was monitored *in situ* by Raman spectroscopy to gain insight into the key reaction steps.

Here we report a DFT study of the deuteration of Pd-activated C(sp^2)–H bonds in palladated azobenzenes described above (Scheme 1). We explore possible D-sources and investigate pathways to the deuterated azobenzene using **Cys^{4D}** as a D-source.



Scheme 1. Deuteration of the palladated azobenzenes.

Financial support was provided by the Croatian Science foundation (grants IP-2019-04-9951 and IP-2020-02-1419). Computations were done on the Isabella cluster at SRCE, Zagreb, Croatia.

References:

[1] (a) J. Atzrodt, V. Derdau, W. J. Kerr, M. Reid, *Angew. Chem. Int. Ed.* **57** (2018) 1758–1784; (b) T. Pirali, M. Serafini, S. Cargnin, A. A. Genazzani, *J. Med. Chem.* **62** (2019) 5276–5297; (c) C. Schmidt, *Nat. Biotechnol.* **35** (2017) 493–494.

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CL 1. On the Interface between Experiment and Computation, the Experimentalist's Viewpoint

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The experimental results stand as fixed points for the testing of accuracy of chemical computational models. On the other side, the structural and physico-chemical insight obtained by the computation often complements the findings obtained by the experiment.

In this talk I will present our integrated experimental-computational approach to the thermodynamic and structural characteristics of organic receptor complexes with ions in solution [1–5]. For the experimental part we used various experimental methods such as isothermal titration calorimetry, absorption, emission and NMR spectroscopies and X-ray structural analysis while for the computational characterization we performed classical molecular dynamics simulations. The overlap of the results obtained by experiment and computation will be emphasized and future perspectives will be also given.

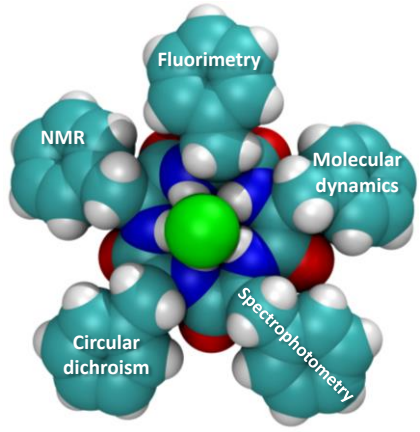

Figure 1. Cyclopentaphenylalanine-anion complexes characterized by experimental and computational methods [1].

Acknowledgements: This work was supported by the Croatian Science Foundation (project Macrosol IP-2019-04-9560) and European Regional Development Fund (project CIuK, KK.01.1.1.02.0016).

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[4] G. Horvat, V. Stilinović, B. Kaitner, L. Frkanec, V. Tomišić, *Inorg. Chem.* **52** (2013) 12702–12712.

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CL 2. Degradation of the Interface Between Fluorinated Polymer Electrolyte and Lithium Metal Anode Using First-Principles Theory

Gaëlle Bouder and Philippe Carbonniere

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Université de Pau et des Pays de l'Adour, E2S UPPA, CNRS, IPREM UMR5254, Institut des Sciences Analytiques et de Physico-chimie pour l'Environnement et les Matériaux, Helioparc, Pau, France

All-solid-state batteries (ASSBs) with an electrolyte polymer have emerged as a promising solution to address the growing demand for efficient energy storage systems and reduce overall energy consumption [1]. These batteries utilize a solid-state electrolyte composed of a polymer material, offering numerous advantages over traditional liquid electrolytes [2]. However, the utilization of a lithium metal anode gives rise to several additional challenges [3]. Furthermore, the intricate relationship between the mechanisms governing metallic lithium deposition and the growth of the electrode-electrolyte interface throughout the battery's lifespan, remains insufficiently comprehended at present.

In the present work, ab initio molecular dynamics (AIMD) simulations [4] and density functional theory (DFT) [5] are employed to investigate the degradation of a fluorinated polymer electrolyte on distinct lithium metal anode surfaces. To this purpose, we realized different systems with isolated molecules of the electrolyte: two solvents, one lithium salt, and one fluorinated polymer with various orientations on lithium surfaces. Initially, we replicated a previously studied system, namely, an EC molecule on a lithium surface, in order to validate our future results [6]. Subsequently, we explored the isolated molecules of the fluorinated electrolyte on the electrode (Fig. 1). The results of this study allow us to gain insight into the key surface reaction pathways that lead to the degradation of lithium electrode and the formation of products such as LiF, which is well-known for inhibiting dendrite growth [2].

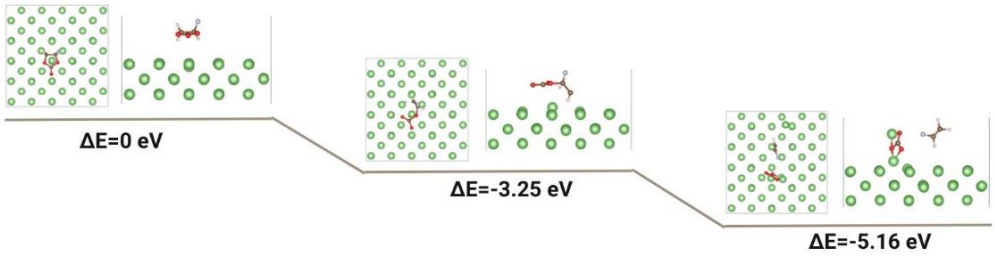

Figure 1. Reduction decomposition products for FEC on Li surface.

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CL 3. Molecular Design and Computational Investigation of Optoelectronic Properties of Conjugated Polymers for OPV Cells

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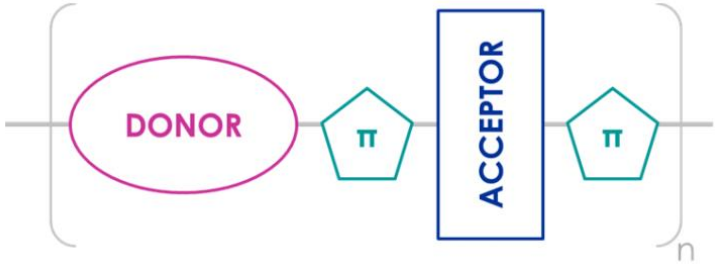
Organic photovoltaic (OPV) cells are a technology that converts solar power into electrical energy and use semiconductor materials as small molecules and donor-acceptor (D-A) copolymers [1]. *Ab initio* modeling is a powerful technique to design materials at the atomistic level and predict electronic properties such as optical and electronic gaps, electronic affinity and ionization potential [2], which are strongly correlated to OPVs performance. As the prediction of these properties are well-known [2,3], in this work we present a theoretical study targeting trends on such properties for a series of compounds, based on density functional theory (DFT) and time-dependent DFT (TD-DFT), using B3LYP functional and 6-31G(d) basis set. The selected conjugated polymers have donor and/or acceptor units and some of them include thiophene units as pi-spacers in the polymer backbone, and our results showed the effect of the polymer chain length, side chains and π-interactions.



Acknowledgments: This work is developed as part of the EDENE program that has received funding from the European Union's Horizon H2020 Research and Innovation under the Marie Sklodowska-Curie Grant Agreement N° 945416. Also, this work was performed using HPC resources from GENCI–IDRIS (Grant 2022-102485) and computer time for this study was provided by the computing facilities of the MCIA (Mésocentre de Calcul Intensif Aquitain).

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CL 4. Aggregation Phenomenon and Effects of Trapped Compounds in Complex Mixture by Molecular Dynamics Simulations

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Complex mixtures are challenging systems for both experimental and theoretical investigations. Analytical techniques such as Gel Permeation Chromatography (GPC) coupled with UV-visible spectroscopy or mass spectrometry allow us to draw a cartography of the molecular composition. To go further in the understanding of the molecular behavior of such systems at the atomic scale, computational approaches such as molecular dynamics simulations are powerful methodologies that can be implemented in a synergetic way along with experimental techniques.

Crude oil and new feedstock systems are good examples of complex mixtures. In particular, the asphaltenes fraction, the heavy-weight fraction of crude oil, defined as the fraction insoluble in n-alkane but soluble in aromatic compounds, was intensively investigated over the last years [1]–[3]. Experimental data indicates that asphaltenes have the ability to adsorb and occlude other oil fractions, including resins, biomarkers, radicals, and even metals. For a thorough comprehension of asphaltene aggregation, it is crucial to consider the presence of these so-called trapped compounds. Nevertheless, there is a notable lack of research from a computational point of view focusing on this aspect in order to get a deeper description of the aggregates structure and the aggregation mechanism. Our investigations aim to propose computational strategies designed to provide a more precise perspective on the influence of these trapped compounds on asphaltene aggregation and the type of interactions involved. In that scope, we implemented all-atoms molecular dynamic simulations and developed a methodology using an annealing procedure to generate ensembles of aggregates with the required sizes and various compositions including trapped compounds. The structure and stability of these aggregates are then analyzed and compared with experimental data. The results show a tendency for most of these trapped compounds to be adsorbed on the surface of the aggregates, while a small fraction is being "occluded".

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CL 5. Computational Chemistry at the Supek Supercomputer

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A number of program packages for computational chemistry is at the users' disposal on the recently launched supercomputer Supek [1]. Beside installation and maintenance, the specialized administration team provides support for optimal exploitation of these programs on the supercomputer. The applications for the common computational tasks will be presented in the lecture with particular attention paid to scalability and reasonable usage on Supek.

Figure 1. The Supek supercomputer.

References:

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CL 6. Insights into the Impact of Gold Nanoclusters $Au_{10}SG_{10}$ on Human Microglia

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Liganded gold nanoclusters with up to hundred gold atoms and biomolecules as ligands can be used in biomedical applications [1]. We present the results on impact of small liganded gold nanoclusters with 10 gold atoms and 10 glutathione molecules as ligands ($Au_{10}SG_{10}$) on several biomarkers in human microglia [2]. We connected the atomically precise structure of $Au_{10}SG_{10}$ with their properties and changes in several biomolecules under oxidative stress. $Au_{10}SG_{10}$ caused the loss of mitochondrial metabolic activity, increased lipid peroxidation and translocation of an alarmin molecule, high mobility group box 1 (HMGB1) [3], from the nucleus to the cytosol. Molecular modeling provided an insight into the location of amino acid in HMGB1 interaction sites with $Au_{10}SG_{10}$ and the nature of bonds participating in these interactions. We show that $Au_{10}SG_{10}$ can bind directly to the defined sites of reduced, oxidized, and acetylated forms of HMGB1. Further studies with similar complementary approaches merging live-cell analyses, determination of biomarkers, and cell functions could lead to optimized gold nanoclusters best suited for diagnostic and bioimaging purposes in neuroscience.

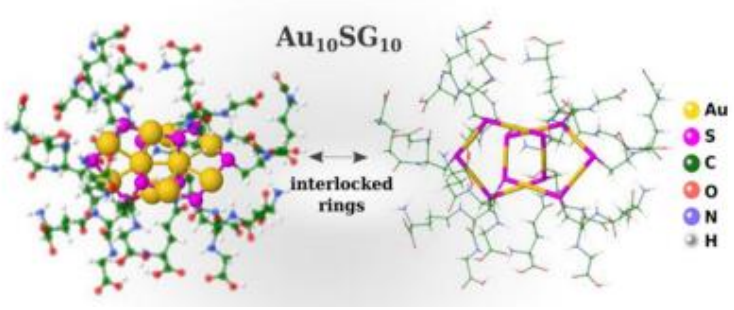

Figure 1. Liganded gold nanoclusters $Au_{10}SG_{10}$.

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CL 7. Characterization of Diamondoid Clusters Emerging in Helium Nanodroplets

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Diamondoids are promising scaffolds in nanomaterial design. We recently prepared diamondoid covalent assemblies, molecules consisting of diamondoid cage subunits connected with a heteroatom or a functional group, and tested their behavior on bulk surfaces [1]. As their spontaneous self-assembly is highly influenced by intermolecular London dispersion interactions, we explored their agglomeration in another medium as well. Namely, we studied the arrangement of diamondoid derivatives in helium nanodroplets (HNDs), an environment suitable for characterizing weakly-bound supramolecular clusters [2]. It was confirmed that their organization in HNDs was indeed predominantly governed by dispersion interactions when derivatives of low polarity (hydrocarbons and ethers) were studied, whereas introduction of more polar functional groups to diamondoid scaffolds resulted in the formation of nanostructured supramolecular networks (Figure 1). Using computational analysis we thereby gained deeper insights into the agglomeration behavior of diamondoid derivatives, making one step further towards understanding the forces governing their self-organization, with important implications for designing next generation of building blocks in nanotechnology.

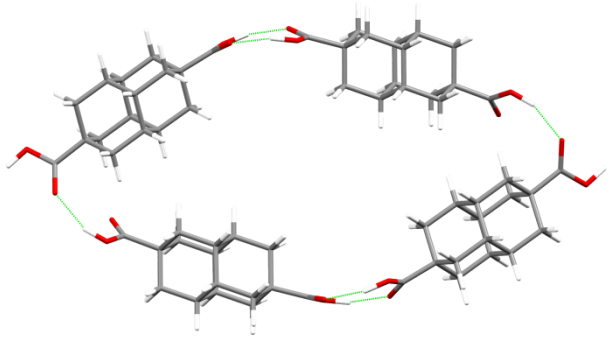

Figure 1. Computed cyclic assembly of 4,9-diamantanedicarboxylic acid molecules formed in HNDs.

Acknowledgements: This work has been supported by the Croatian Science Foundation (UIP-2017-05-9653).

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CL 8. A Machine Learning Approach to Study of Thermosalient Molecular Crystals

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Thermosalient materials change size dramatically when heated or cooled. Their crystals go through a rapid and energetic transition where they jump to distances much bigger than their original size.

The computational study of the thermoslient effect in materials requires a high level of accuracy that can only be achieved through ab-initio techniques such as DFT. However, accurately simulating systems of this size demands a lot of computational power, which makes such calculations impractical. Fortunately, recent developments in machine learning, specifically equivariant graph neural networks [1] make it possible to create accurate machine learning interatomic potentials (MLIPs) efficiently. In this way, we can approach the accuracy level of DFT while benefiting from linear scaling akin to classical potentials.

Starting with just three experimental structures that represent the phases of the molecular crystal, an efficient and versatile dataset was created using normal mode sampling and then further improved using active learning. After reaching the plateau in the improvement of the potential this MLIP was used for calculations of free energy using the harmonic approximation and quasi-harmonic approximation. This way we can explain experimentally observed phase transitions and gain a better understanding of thermosalience.

Acknowledgement: This work has been supported by Croatian Science Foundation under the project UIP-2020–02-5675.

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Posters

P 1. Quantum Mechanics/Molecular Mechanics: Powerful Tool for Investigating Noble Metal Liganded Nanoclusters for Bio-Applications

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Nanoscience followed by computational chemistry have become very valued and beneficial research pathways in recent decades [1, 2]. The reason for this is the plethora of physical properties hidden between scale 1 and 100 nm. This fits right in the famous lecture "There is Plenty of Room at the Bottom" by the physicist Richard Feynman [3]. Atomically precise metal quantum clusters - nanoclusters (NCs) have attracted great interest in bio-applications due to their attractive properties such as ultra-small size, low toxicity, photostability, intense photoluminescence, and excellent biocompatibility. Among the noble metal NCs those of gold and silver are the most researched due to their versatile applications. Noble metal NCs are inadequate to perform alone as biosensors since they dissolve in the biological environment failing to maintain their structural and optical properties. Their bio-application is based on functionalization by various biological molecules that not only protect them from the environment keeping them intact but also offer target-recognition specificity, reduced toxicity and enhancement of their emissive properties.

Time-dependent density functional theory (TDDFT) brings research closer to the origin of optical properties on liganded noble metal NCs and bio-nano hybrids. QM/MM method was a beneficial approach in this research for determining structural and optical properties of liganded noble metal nanoclusters and bio-nano hybrid systems by considering full ligands and the biological environment. The examples of the QM/MM approach on liganded noble metal NCs will be presented.

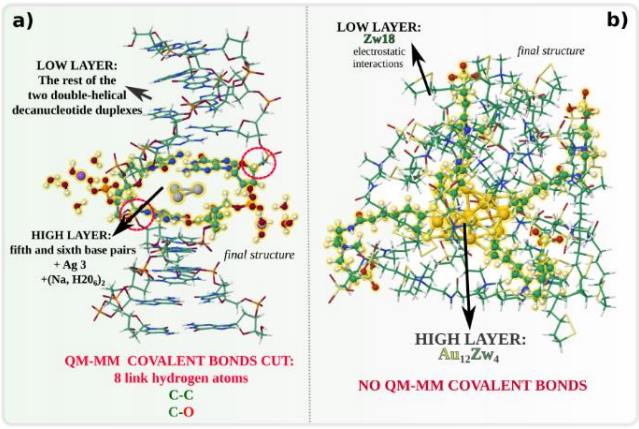

Figure 1. Examples of two-layer ONIOM method: a) $Ag3$ cation intercalated in DNA structure [4] and b) liganded gold nanocluster $Au12$-$Zwitterions4$ in bioenvironment [5]

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P 2. Trajectory Maps: Protein Molecular Dynamics Visualization and Analysis

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Molecular dynamics simulations generate trajectories that depict system's evolution in time and are analyzed visually and quantitatively. Commonly conducted analyses include RMSD, Rgyr, RMSF, and more. However, those methods are all limited by their strictly statistical nature. Here we present trajectory maps, a novel method to analyze and visualize protein simulation courses intuitively and conclusively. By plotting protein's backbone movements during the simulation as a heatmap, trajectory maps provide new tools to directly visualize protein behavior over time, compare multiple simulations, and complement established methods (Figure 1). A user-friendly Python application developed for this purpose is presented, alongside detailed documentation for easy usage and implementation[1]. The method's validation is demonstrated on two case studies of protein simulations from the literature[2,3], and another set of simulations prepared for the study. Considering its benefits, trajectory maps are expected to adopt broad application in obtaining and communicating meaningful results of protein molecular dynamics simulations in many associated fields such as biochemistry, structural biology, pharmaceutical research etc.

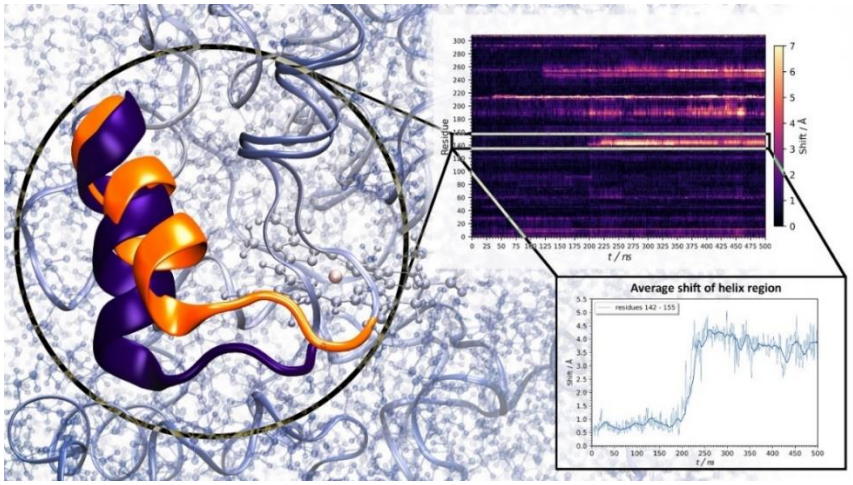

Figure 1.

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P 3. Molecular Modeling Study of Sonic Hedgehog Protein Interaction with Sex Hormone Receptors

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Sonic Hedgehog (SHH) is one of three Hedgehog (HH) ligands expressed in mammals that initiates the canonical Hedgehog-GLI (HH-GLI) signaling pathway involved in embryonic development, stem cell maintenance and tissue homeostasis [1]. To become a fully active signaling molecule (SHH-N), a cholesterol moiety and a palmitoyl group are added to the C- and N-termini of its signaling (N-terminal) domain, respectively. Aberrant activation of the HH-GLI signaling pathway in adult cells is associated with the development of various tumors, including sex hormone-sensitive cancers like breast and prostate cancer [2]. Our previous studies [3] demonstrated a potential direct link between SHH and estrogen receptor alpha (ERα) and androgen receptor (AR). Namely, according to our research, SHH can bind ERα and AR and activate them in non-canonical manner. This might be a mechanism that enhances survival of breast and prostate cancer cells that express SHH, even in conditions of estrogen and androgen deficiency, respectively. As a continuation of these studies, here we also examined the possibility of binding of the C-terminally cholesteroylated N-terminal domain of SHH to the progesterone receptor (PR), the remaining member of the group of sex hormone receptors.

Molecular modeling study was performed to investigate the possibility of cholesterol binding, free or bound to the SHH-N C-terminal, with sex hormone receptors (ERα, PR and AR), and to test and compare the stability of the formed complexes. As a positive control, molecular dynamic (MD) simulations of ERα and PR in complex with the steroid hormone responsible for its activation in the cell, i.e., ERα – estradiol (E2) and PR – progesterone complexes, were conducted. Since we had no prior knowledge of the residues involved in protein-protein (PP) interactions in the complexes, we performed a PP docking study using the Hdock server (http://hdock.phys.hust.edu.cn/) to predict binding complexes. For individual complexes, MD simulations were performed for a duration of at least 0.5 μs. A molecular modeling study revealed the molecular details of these interactions, while free energy calculations (MM/G(P)BSA approach) helped us to investigate which non-canonical interaction of the sex hormone receptor with the C-terminal cholesterolylated N-terminal domain of SHH is more likely.

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P 4. Structural Differences of Symmetric and Asymmetric Mixed-Lipid Bilayers Observed by Classical Molecular Dynamics

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Accurate modeling of eukaryotic plasma membranes is a challenging endeavor due to the compositional asymmetry of the phospholipid bilayer in biological systems [1]. Asymmetric membranes, which contain different lipids in upper and lower leaflets, are difficult to prepare and characterize experimentally [2]. Thus, molecular dynamics (MD) simulations may be employed to provide insight into structural organization and hydration. In this study, classical MD simulations were used to compare structural properties and arrangement of symmetric and asymmetric membranes consisting of 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC) and 1,2-dipalmitoyl-*sn*-glycero-3-phosphoserine (DPPS), in gel and fluid phase. The asymmetric membrane was generated by surface area matching to minimize the mismatch between upper and lower leaflet packing. All simulations were conducted in GROMACS, using the CHARMM36m force field, for a total of 200 ns of production. Parameters such as area per lipid, membrane thickness, acyl chain order and lipid lateral diffusion were analyzed in order to describe structure and organization. The study showed that lipid organization and ordering are significantly affected when the two lipids are mixed within the single leaflet, and much less so when leaflets contain only one component. There was also an indication of packing differences affecting hydration. Obtained results provided invaluable insight into different behavior of symmetric and asymmetric systems also observed experimentally.

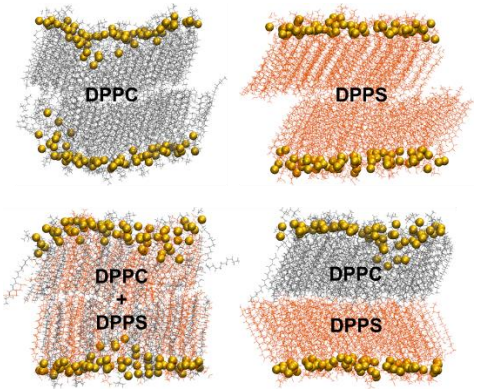

Figure 1. Representative snapshots of pure (top) and mixed-lipid bilayers (bottom). Mixed-lipid bilayers may be symmetric (left) or asymmetric (right).

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P 5. Building Potential Energy Surfaces from Quantum Chemical Docking by Deep Reinforcement Learning

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Alzheimer's disease is a neurological disorder characterized by the progressive death of nerve cells in the brain, resulting in the loss of the individual's cognitive abilities. Unfortunately, no drugs are available at this time to prevent the development or reduce the progression of this disease. There are several hypotheses that try to explain the cause of Alzheimer's disease, and one of them is the cholinergic hypothesis [1]. To increase the level of acetylcholine in the brain of affected individuals, cholinesterase inhibitors have begun to be developed as therapeutics of acetylcholinesterase (AChE) (known physiological roles) and butyrylcholinesterase (BChE) (so far unknown roles) [2].

Multiple simultaneous quantum-mechanical docking [3] of small molecules is determination of the most energetically favorable mutual configurations of one, two or more molecules. It includes explicit consideration of the electronic structure of molecules, which is necessary for a correct understanding of interactions between a protein and its ligand. However, the application of quantum-mechanical docking also requires considerable computer time and methods for reducing calculation period are very desirable. Deep reinforcement learning is a special form of neural network (NN) training in which the network is gradually trained on an increasingly large set of training data while monitoring the mean squared error of estimation on a set of data that was not used for training (validation set) [4]. This enables the NN as a universal regressor to correctly reproduce the basic function that connects input and output data without overfitting the network. This type of deep learning will be utilized for the representation of potential energy surface obtained by quantum chemical docking of formaldehyde into the active site of BChE. The obtained results will be presented, and computational demands discussed.

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P 6. Molecular Dynamics Simulations of Selected Homocyclopentapeptides with Chloride, Bromide and Iodide Anions

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Cyclopeptides are a class of ion-receptor compounds that comprise a bonding site geometrically suitable for selective bonding of anions [1]. The ability of these compounds to transport anions through cell membranes makes them a target of pharmaceutical research [2].

In our investigations we have estimated Gibbs free energies of complexation reactions of cyclopentaleucine, cyclopentaphenylalanine and cyclopentaserine with chloride, bromide and iodide anions in acetonitrile and methanol by means of alchemical transformations. In these simulations we have constructed the complexation process by crossing a path of unphysical intermediate states that connect the end states. The first two cyclopeptides were chosen to test the method against experimental data and the third one was used to estimate the effect of additional hydroxyl groups on complexation [3]. The Gibbs energy estimation was performed using the Bennett acceptance ratio (BAR) for dissociation of cyclopeptide-anion complexes, substitution of the anion of such complexes as well as for mutation of side-chains of the ligand [4]. Simulations were performed by Gromacs2022.5 with OPLS-AA and CHARMM36 force fields.

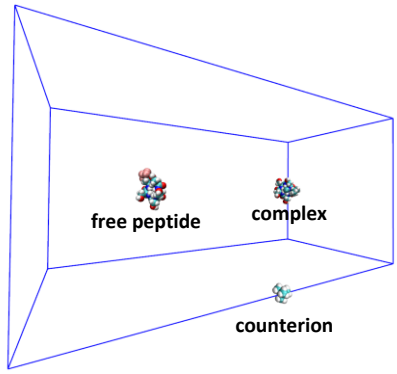

Figure 1. The system comprising a cyclopeptide-ion complex undergoing an alchemical transformation, a free cyclopeptide undergoing a reverse alchemical transformation and a counterion. Solvent molecules are omitted for simplicity.

Acknowledgements: This work was supported by the Croatian Science Foundation under project IP-2019-04-9560 (Macrosol) and European Regional Development Fund (project CIuK, KK.01.1.1.02.0016).

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P 7. Experimental and Computational Study of Phase Transformations and Magnetism in a Copper Carboxylate

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Periodic Density Functional Theory (pDFT) has been extensively used to explain and predict the structure and properties of crystalline materials, including Metal Organic Frameworks (MOFs) [1]. It can predict relative thermodynamic stabilities, calculate magnetic properties, and give structural information.

We have recently shown [2] that complexes of Cu(II) and Zn(II) with 2,5-dioxido-1,4-benzenedicarboxylic acid (H_4**dobdc**) can serve as precursors for the archetypal MOF-74 [3] family of MOFs. Importantly, the products' magnetic properties depend significantly on the metal carboxylate used in the synthesis, likely due to their differing thermodynamic stabilities. In addition, the metal carboxylates themselves, especially the copper carboxylate Cu-INT, show interesting magnetic properties.

We, therefore, decided to study these carboxylates further experimentally (PXRD, FTIR, TGA) and through pDFT. We discovered unexpected phase behavior in Cu-INT upon evacuation (Cu-INT-vac), and pDFT calculations were able to predict the existence and structure of the thermodynamically most stable form. Magnetic properties of the different phases were studied by ESR spectroscopy and magnetometry, and their thermodynamic stabilities gave new insight on the differences between the (Zn,Cu)-MOF-74 phases.

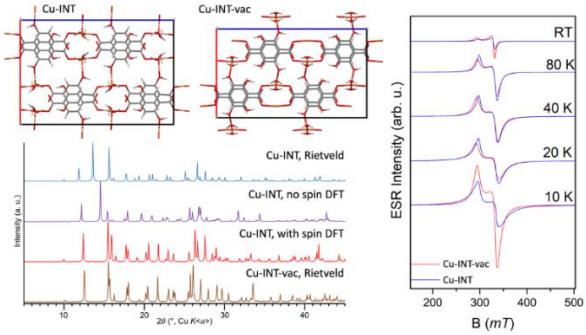

Figure 1. The crystal structures of Cu-INT phases. Comparison of PXRD patterns for experimental and pDFT calculated Cu-INT phases. ESR spectra of Cu-INT and Cu-INT-vac at different temperatures

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P 8. Thermomechanical Properties of Molecular Crystals from Machine Learning Potentials

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Molecular crystals are a common and important class of crystalline materials. However, modeling molecular crystals based on first principles (eg. with density functional theory) is often difficult due to the size of a typical unit cell. Therefore, high-throughput calculations for the discovery of useful properties are rare. Mechanical and thermal properties are even harder to model correctly as a standard harmonic approximation is often not accurate enough.

We show how machine-learned interatomic potentials can enable accurate and fast calculations of mechanical and thermal properties of molecular crystals enabling a high-throughput search for materials with the desired properties. In principle, to train machine learning potential one would need to create a sufficiently large database of molecular crystals calculated with the desired accuracy. This is also a very challenging task and we will show how to avoid this step using transfer learning and existing databases of small systems.

P 9. Full Conformational Analysis of Cashmeran by Principal Component Analysis of Molecular Dynamics Trajectory

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The potential energy surface of the fragrant compound cashmeran was sampled by *ab initio* molecular dynamics [1]. Initially, the trajectory was spanned by Cartesian coordinates and then transformed into distance coordinates that do not depend on the orientation of the molecule. Complete conformational analysis was performed by tensor decomposition of molecular dynamics trajectory [2]. 2nd-order tensor decomposition tool principal component analysis was used as a dimensionality reduction method [3] and a total of 10 dimensions in the newly formed reduced space were retained (describing 75% of the total variance). For these 10 dimensions, the probability distribution function was generated. A brute force combinatorial algorithm was applied to search all strict local maxima of the obtained function and initial guess structures were generated from these maxima points. All generated structures were optimized at the B3LYP/6-31G(d) level of the theory using Grimme's D3 dispersion correction [4] using the Gaussian 16 software [5]. After optimizations and clustering, a total of 5 conformers was obtained where the two lowest energy conformers were prevailing in content (>99% according to the Boltzmann distribution at room temperature).

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P 10. Quantum-Chemical Docking of Small Bioactive Molecules into the Active Site of Butyrylcholinesterase

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An important characteristic of Alzheimer's disease is the loss of neurotransmitters, which are molecules that transmit signals between nerve cells in the brain. One of the most important neurotransmitters affected in Alzheimer's disease is acetylcholine. A reduction in acetylcholine levels in the brain is thought to contribute to memory loss and cognitive decline that are hallmarks of the disease [1]. Butyrylcholinesterase (BChE) and acetylcholinesterase (AChE) are enzymes that play a crucial role in the metabolism of acetylcholine. They are both hydrolytic enzymes that catalyze the hydrolysis of acetylcholine, a process that breaks down acetylcholine into its components, acetate and choline. Butyrylcholinesterase is responsible for the breakdown of acetylcholine in the bloodstream and other tissues, but not so much in the brain of a healthy person. However, BChE activity gradually increases in patients with Alzheimer's disease, while AChE activity remains unchanged or decreases [2]. Inhibiting BChE could help treat Alzheimer's disease and therefore molecular docking was carried out.

Small bioactive aziridine and azetidine molecules were selected and docked into the active site of BChE using quantum-chemical docking [3]. A systematic search of the configuration space was performed using a Monte Carlo algorithm that includes all translational and rotational degrees of freedom of the molecules. For selected top 100 local minima, the geometry was optimized using the QM/QM approach within the ONIOM (B3LYP-D3/6-31G(d):PM7) formalism [4]. Binding energies were calculated and compared for both compounds, and their synergistic effect was tested by adding another molecule of the same type to the active site.

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P 11. Vibrational Tunneling Spectra of the Water Hexamer Prism

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The water hexamer is an assembly of six water molecules that are weakly bound by hydrogen bonds. This particular cluster is probably the most intriguing one out of a plethora of other studied water clusters because it is the smallest one with 3D structure. Studying water clusters is of great importance because the behavioral essence of intermolecular forces between the water molecules in cluster mimics that of the bulk.

At very low temperatures, molecules in the cluster can rearrange and generate new, equivalent structures. These structures are connected to one another by some symmetry operation. It is observed that the water hexamer system has a great number of possible minima, but only the ones connected by short and energetically accessible tunneling paths cause significantly observable splittings, which exhibit a characteristic doublet-of-triplets pattern in the spectrum [1]. The explanation of the specific splitting pattern is found to involve the two main tunneling pathways: antigeared and geared (Fig. 1.) [2].

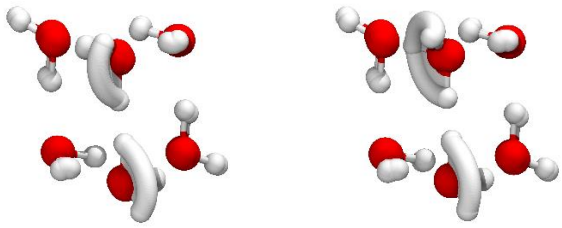

Figure 1. The two main tunneling pathways: antigeared (left) and geared (right).

The method used for calculating the tunneling splittings is based on instanton theory. In order to obtain the ground-state splitting, the procedure involves constructing a WKB wavefunction along the instanton path and its harmonic surroundings for each well and putting the acquired wavefunction in the Herring formula which ultimately results in tunneling splitting. The excited state splittings are generated using an analogue approach [3].

The main advantage of this method lies in its applicability to determining both ground- and excited-state splittings. Ring polymer instanton theory and path integral molecular dynamics can only calculate tunneling splittings in the ground state. Another great advantage of the presented method is its appropriateness for mid-large systems in full dimensionality and the possibility of combining it with on-the-fly methods for electronic structure calculations.

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P 12. When Position Matters – Different Photophysical Properties of Two Regioisomers Based on Imidazo[4,5-*b*]pyridine

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Nitrogen-containing heterocycles are, besides their well-known biological features, recognized as an interesting class of organic fluorescent sensors present in a wide range of (bio)chemical and environmental processes. Due to their excellent spectroscopic properties and diverse spectral responses, such derivatives offer promising applications in optoelectronics as optical lasers, fluorescence probes, organic luminophores and fluorescent dyes [1].

Here we present the synthesis of two regioisomers based on imidazo[4,5-*b*]pyridine that differ only in the position of the pyridine nitrogen, whose photophysical and chemical properties were studied using a range of spectroscopic and computational techniques in order to inspect their potential as pH sensing materials. Their synthesis was initiated by the condensation of 2-cyanomethylimidazo[4,5-*b*]pyridine with 2-chlorobenzoyl chloride to the acyclic precursor. With a two-step thermic cyclization, this led to the chloro-substituted tetracyclic precursors, and, subsequently, to both amino substituted regioisomers **A** and **B** employing the uncatalyzed microwave assisted amination. Their spectroscopic characterization was achieved by UV/Vis and fluorimetric spectroscopies in 11 organic solvents and water. This revealed interesting features that significantly differ among regioisomers. Computational analysis at the B3LYP/6–31+G(d) level with implicit SMD solvation focused on determining the precise pK_a values and their protonation states in water, and aided in interpreting the recorded UV/Vis spectra, which all confirmed the potential of studied molecules to probe the pH conditions in solution.

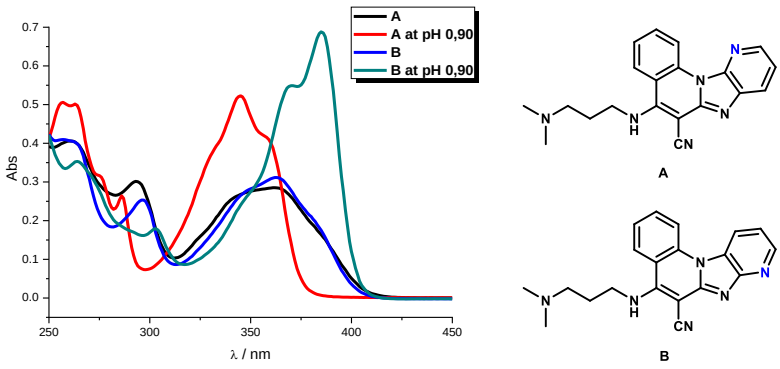

Figure 1. Structures of studied regioisomers and their absorption spectra at neutral and acidic conditions.

Acknowledgment: This work was funded by the Croatian Science Foundation (IP-2020-02-8090).

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P 13. DMF – a solvent, an acid, or an electrophile?

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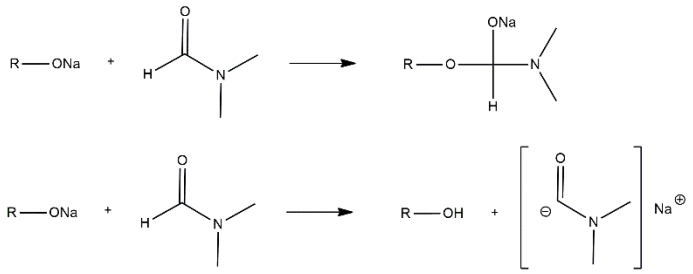
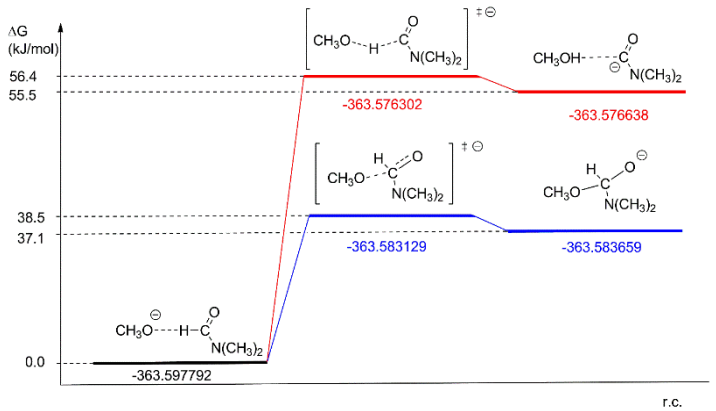
When dimethylethynylmethanol (R = $C(CH_3)_2CCH$) is dissolved in dimethylformamide (DMF), the latter behaves as expected – as an organic solvent. The same applies to a series of other alcohols. However, if an alcohol is converted to an alkoxide form, the role of DMF is changed – it can react as an acid, or as an electrophile (Scheme 1).



Scheme 1. Addition of alkoxide to DMF (first row), and acid-base equilibrium between the two.

In this study we use quantum-chemical calculations to investigate the mechanism underlying these reaction pathways. Methoxide anion (without counterion) has been used as a model to describe the corresponding energy surfaces (Scheme 2).



Scheme 2. Energy diagram for the deprotonation of DMF (red line) resulting in the carbamoyl anion-methanol complex product, and the addition of methoxide to DMF (blue line) resulting in the amide acetal intermediate. Gibbs free energy values (in Hartrees) were calculated at the SCRF(SMD)-M06L/6-31+G(d,p) level of theory (in DMF as a model solvent).

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Notes

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