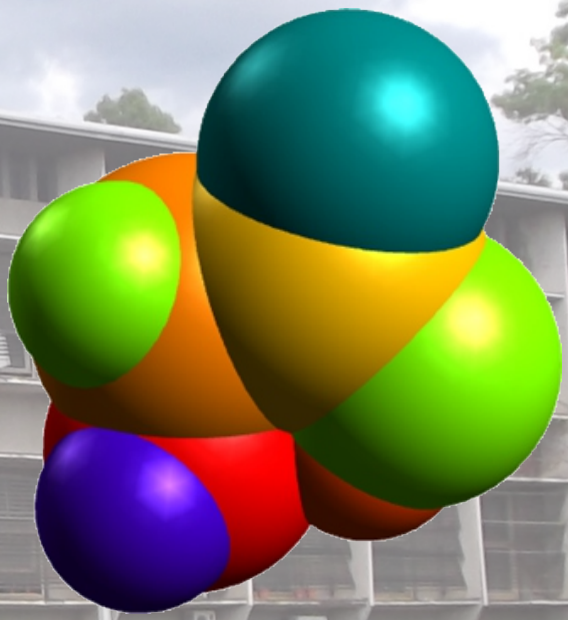
Computational Chemistry Day 2022



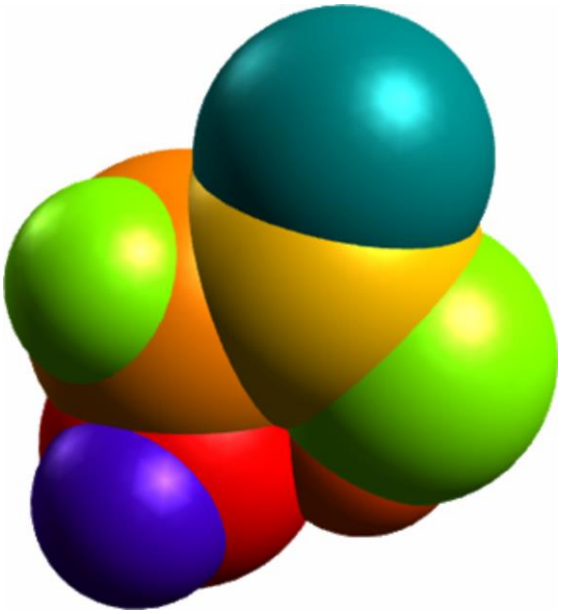
Book of abstracts

Ruđer Bošković Institute

September 24th, 2022

Zagreb, Croatia, EU

Computational Chemistry Day 2022



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Foreword

Computational Chemistry Day, CCD, is an annual meeting that gathers Croatian computational and theoretical chemists. Due to the pandemic, CCD has been postponed for two years. Even this year, the usual meeting date in May was derailed by the pandemic; therefore, we are getting together exceptionally in September.

Each meeting confirmed that these events are indeed needed and very useful for information and knowledge sharing, as well as for social networking and establishing new collaborations. Even with so diverse forms of communication available today, live socializing cannot be replaced by anything else. The minimalistic formula of the meeting: a single day, ten lectures, twenty posters, and socializing after the official close-up, was recognized as well-chosen. Also, Saturday, as the meeting day, turned out to be a good decision due to easier access to the lecture rooms and parking lots. Yet, we are ready and willing to hear different opinions.

We are still ambitious to introduce other kinds of activities, like workshops and courses, and we will continue to endeavor to achieve this goal. However, we realized that more time is needed for their development and implementation. We encourage all those wishing to deliver a lecture at the meeting to contact the organizers. Young scientists with Ph.D. or close to finishing it are especially welcome.

This year the meeting will be held at the Ruđer Bošković Institute (RBI), the institution with the most computational chemists and the longest history in computational chemistry in Croatia. It is noteworthy that the computational and theoretical chemistry fields in Croatia were introduced just at RBI. The *Group for theoretical chemistry* was founded in 1963, but the research in the field had already begun in 1959. The computational chemistry in Croatia is, therefore, at least 60 years old. The Group's first leader was Milan Randić, and the first members were Zvonimir Maksić and Zlatko Meić. The Group was soon joined by Nenad Trinajstić, Tomislav Cvitaš, Ante Graovac, Tomislav Živković, Slobodan Bosanac, and Aleksandar Sabljić, who remained the core members for decades to come. The Group was known for its high scientific production and extensive collaboration with scientists worldwide. Although computational resources were scarce at the time, the research in the Group involved computational aspects from the beginning, with Zvonimir Maksić being the most prominent member. The first licenses for the *Gaussian* package were purchased by him. He later founded the *Group for quantum chemistry*, which became the first computational chemistry group in the modern sense. We use this opportunity to mention the names of the first protagonists in the field as a homage to their initiative and enthusiasm.

Computational resources are indispensable in our discipline. Fortunately, some twenty years ago, the *University computing centre SRCE* of the University of Zagreb restored its role in providing computational resources to the academic community and started to build a common computational infrastructure. Since then, the computational capacities have been maintained at a high professional level and, on several occasions, expanded and enriched. The last endeavor of SRCE, the HR-ZOO project, financed mainly through EU funds, will increase the computational capacities by an order of magnitude. This expansion will allow us, at least for some time, to concentrate on our projects without concern for the necessary computational resources. We very much appreciate the effort and expertise that SRCE invested in the realization of this

project. At the same time, we would like to invite all users to responsible and thoughtful utilization of the resources at our disposal in a rarely accessible way.

Finally, we owe a word of gratitude to our sponsors and donators. So far, each year, we have had a lecturer from *Selvita d.o.o.* (previously *Fidelta d.o.o.*) that provided us with direct contact with computational endeavors in the pharmaceutical industry. In purchasing computational resources, RBI has long-standing partner relations with *O2 d.o.o.*, *S&T d.o.o.,* and *Informos d.o.o.* They confirmed themselves as fair players who tend to achieve a quality of service and client satisfaction equally as their success. *Croatian Science Foundation* supported the organization of this meeting from the very beginning, as well as the *Ministry of Science and Education*.

The Organization Board of the *Computational Chemistry Day 2022*

Program of the *Computational Chemistry Day 2022*

08:45–09:00 ***Opening addresses (3rd wing, the lecture room)***

1st session (moderator: **Ines Despotović**)

09:00–09:30 **Luca Grisanti** (IRB, Zagreb)
Multiscale Modeling of Organic and Bio-materials: Energy Transfer and Molecular Excitons (IL)

09:30–10:00 **Davor Šakić** (FBF, Zagreb)
Shining Light on the Old Reaction; Reneissance of the Hofmann–Löffler–Freytag Reaction (IL)

10:00–10:20 **Davor Oršolić** (IRB, Zagreb)
Compound-Kinase Binding Affinity Prediction with Confidence Guarantees (CL)

10:20–10:40 **Ana Mikelić** (PMF-KO, Zagreb)
Evolution of Inhibition Models for Fluorinated Cinchona *Alkaloids by Machine Learning (CL)*

10:40–11:10 ***Coffee break***

2nd session (moderator: **Robert Vianello**)

11:10–11:40 **Sanja Koštrun** (Selvita, d.o.o, Zagreb)
Macrolide Inspired Macrocycles as Effective Disruptors of the IL-17A/IL-17RA Interaction (IL)

11:40–12:10 **Branimir Bertoša** (PMF-KO, Zagreb)
Computational Study as Guideline for Experimental Research (IL)

12:10–12:30 **Jurica Novak** (OBT, Rijeka)
Computational Chemistry Artillery Against Viruses (CL)

12:30–12:50 **Emir Imamagić** (Srce, Zagreb)
Project HR-ZOO - The Final Stages of Implementation (CL)

12:50–14:00 ***Lunch break (1st wing, corridors on the ground floor)***

3rd session (moderator: **Nađa Došlić**)

14:00–14:30 **Marko Cvitaš** (PMF-FO, Zagreb)
Vibrational Tunneling Spectra of Molecules via Instanton Theory (IL)

14:30–14:50 **Mihael Eraković** (IRB, Zagreb)
Substituent Effect on Tunneling in Heterodimers of Benzoic Acids (CL)

14:50–15:10 **Jiangyang You** (IRB, Zagreb)
Modelling Electron Spin Decoherence at Low Temperatures (CL)

15:10–15:30 **Aleksandra Maršavelski** (PMF-KO, Zagreb)
How Norvaline Affect the Stability of Secondary Protein Structures – a Computational Study (CL)

15:30–15:50 **Tomislav Piteša** (IRB, Zagreb)
How to Interpret Trajectory Surface Hopping Dynamics? (CL)

15:50–16:00 ***Concluding remarks***

16:00–18:00 ***Poster session (1st wing, corridors on the ground floor)***

18:00–22:00 ***Party near the pool***

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

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Lectures

IL 1. Multiscale Modeling of Organic and Bio-materials: Energy Transfer and Molecular Excitons

Luca Grisanti

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Multi-scale or hybrid modeling strategies are nowadays a successful tool in modeling different kinds of properties and processes in molecular and bio- materials. In these systems, the interactions between molecular units have a strong impact on the properties, but a full modelization from first principle is generally prohibitive due to size and/or the complexity of the systems. As an example, the interaction between electronic excited states is manifested in phenomena such as energy transfer and excitonic effects.

In Resonance Energy Transfer (RET) the energy is transferred from an excited molecule, called the energy donor (D), to an acceptor molecule (A). We combined DFT and TD-DFT results with an extensive equilibrium and non-equilibrium molecular dynamics (MD) of a bound *D*–*A* pair in solution to build a coarse-grained kinetic model [1]. A thorough MD study is needed to properly address RET: the large configuration space visited by the system cannot be reliably sampled accounting only for a few representative configurations. Moreover, the conformational motion of the RET pair, occurring in a similar time scale as the RET process itself, leads to a sizable increase of the overall process efficiency.

Excitonic interactions are another fundamental ingredient of many processes from nature to devices, that can be evaluated at different levels of theory [2]. We are working on a development of a hybrid scheme that allows us to describe optical properties of molecular crystals and where the geometric features of excitonic interactions are crucial [3]. We preliminary tested our scheme on a material exhibiting crystallochromism.

Acknowledgement: Research supported by Croatian Science Foundation “Hybrid modeling for excited states in novel molecular materials: from optical properties to exciton dynamics”, HYMO4EXNOMOMA, IP-2020-02-7262.

References:

[1] M. Anzola, C. Sissa, A. Painelli, A. A. Hassanali, and L. Grisanti, *J. Chem. Theory Comput.* **16** (2020) 7281–7288.

[2] (a) Z. You, C. Hsu, *Int. J. Quantum Chem.* **114** (2014) 102–115; (b) L. Grisanti, Y. Olivier, L. Wang, S. Athanasopoulos, J. Cornil, D. Beljonne, *Phys. Rev. B* **88** (2013) 035450.

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IL 2. Shining Light on the Old Reaction; Renaissance of the Hofmann-Löffler-Freytag reaction

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Remote C-H functionalization of unreactive sites is a hot topic in the field of modern synthetic chemistry. Currently, transition metal catalysis is used for regio- and stereo-selective modification and introduction of novel functional groups in compounds. Focus has now turned toward reaction sequences that omit usage of metal catalysts, and there is a resurgence of interest in Hofmann-Löffler-Freytag (HLF) reaction, discovered in 19th century. This reaction enables the formation of new compounds according to the principles of green chemistry, in an environmentally friendly manner with highly efficient syntheses. Numerous computational and experimental studies have shown exceptional flexibility and the possibility of optimising this method in order to increase the economy and reduce the amount of waste generated as by-products of synthetic processes. However, the mechanism of this reaction is yet to be elucidated sufficiently, and further experiments are necessary in order to determine the thermodynamic and kinetic parameters that control and guide the HLF reaction. Computational insights in reaction mechanism, with influence of substituents on 1,5-HAT or 1,6-HAT regioselectivity in HLF reactions will be presented.

IL 3. Macrolide Inspired Macrocycles as Effective Disruptors of the IL-17A/IL-17RA Interaction

Sanja Koštrun,[a] Andreja Fajdetić,[a] Dijana Pešić,[a] Karmen Brajša,[a] Vlatka Bencetić Mihaljević,[a] Dubravko Jelić,[a] Adriana Petrinić Grba,[a] Ivaylo Elenkov,[a] Renata Rupčić,[a] Samra Kapić,[a] Ivana Ozimec Landek,[a] Kristina Butković,[a] Ana Grgičević,[a] Dinko Žiher,[a] Ana Čikoš,[a] Jasna Padovan,[a] Gordon Saxty,[a] Kevin Dack,[b] Håkan Bladh,[b] Tine Skak-Nielsen,[b] Simon Feldbaek Nielsen,[b] Maja Lambert[b] and Martin Stahlhut[b]

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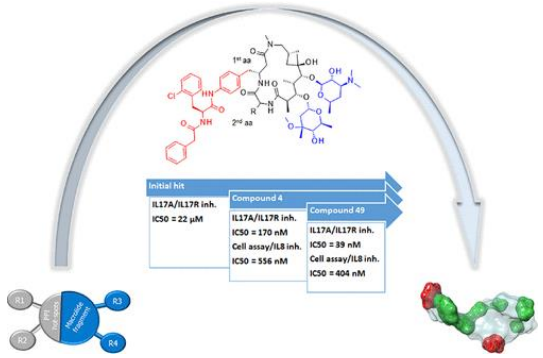
Interleukin 17 (IL-17) cytokines promote inflammatory pathophysiology in many autoimmune diseases, including psoriasis, multiple sclerosis, rheumatoid arthritis and inflammatory bowel disease. Such broad involvement of IL-17 in various autoimmune diseases makes it an ideal target for drug discovery. Psoriasis is a chronic inflammatory disease characterized by numerous defective components of the immune system. Significantly higher levels of IL-17A have been noticed in lesions of psoriatic patients, if com-pared to non-lesion parts. IL-17A/IL-17 RA interaction surface is, as other protein-protein interactions, characterized with hot-spots spread over the wide and flat protein surface. Such interaction sites are mainly intractable with traditional small molecule drugs. This has resulted in efforts to exploit the chemical space of natural products and macrocyclic molecules.

Presented work is focused on the macrolide inspired macrocycles as potential IL-17A/IL-17RA modulators and covers the molecular design, synthesis, and *in vitro* profiling. Macrocycles are by coupling the macrolide fragments with variety of natural or synthetic fragments ranging from amino-acids known to interact with PPI hot-spots, different heterocycles, alkyl substituents or sugars.



Macrocycles, as potential IL-17A modulators, are designed to diversify and enrich chemical space through different ring sizes, stereochemistry combinations and side-chains modifications resulting in the variety of three-dimensional shapes. Structural insights into possible binding interactions have been used to design and prioritize target molecules. Inhibitors in the nM range were identified in both target based and phenotypic assays. *In vitro* ADME as well as *in vivo* PK properties will be discussed.

This work contributes to the body of literature demonstrating that preparation of diverse synthetic and semi-synthetic macrocyclic compounds as modulators of challenging protein–protein interactions is an effective strategy to bridge the space between biologicals and small molecules.

IL 4. Computational Study as Guideline for Experimental Research

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Nowadays millions of tons of inadequately or insufficiently treated sewage, industrial and agricultural waste are released directly into the groundwater, rivers, lakes, seas and oceans, thus introducing numerous species of pathogenic agents. This contamination affects our natural ecosystems and directly affects different food and beverage manufacturing processes. Therefore, detection of pathogens in water must meet specific quality requirements. The current procedures rely on time consuming bacterial culture plating methods or (to a much smaller extent) using expensive molecular methods such as Enzyme Linked Immunosorbent Assays (ELISA), reporter enzyme-dependent detection and Polymerase Chain Reaction (PCR). The main goal of the presented research is to contribute to the development of a novel pathogen detection assay for monitoring water safety that relies on horseradish peroxidase (HRP), an enzyme that was shown to have great potential in the development of novel protein-fragment complementation assays [1].

In order to achieve this goal, combined research consisting of experimental and computational methods is being conducted. The role of computational methods is to provide a deeper understanding of experimental data and to enable insights into the systems of interest at a molecular level. The results of computational simulations pointed to the effect of glycosylation on structural and dynamical properties of HRP which influence its overall stability. Of particular interest is the propagated effect of glycosylation on electrostatic properties of the inner core of the enzyme [2]. These results helped in resolving experimental issues. Further, experimental attempts to attach a single stranded DNA oligonucleotide to the HRP, which is necessary for the development of the proposed pathogen detection assay, were supported by computational simulations. The availability of different enzyme functional groups for oligonucleotide attachment was studied by molecular dynamics simulations. The results of simulations aided the experimental attachment of the oligonucleotide and showed that it should not have significant influence on enzymatic activity, which was experimentally confirmed.

References:

[1] S. Škulj, A. Barišić, N. Mutter, O. Spadiut, I. Barišić, B. Bertoša, *Comput. Struct. Biotechnol. J.* **20** (2022) 3096–3105.

[2] J. D. Martell, M. Yamagata, T. J. Deerinck, S. Phan, C. G. Kwa, M. H. Ellisman, J. R. Sanes, A. Y. Ting, *Nat. Biotechnol.* **34** (2016) 774–780.

IL 5. Vibrational Tunneling Spectra of Molecules via Instanton Theory

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In molecular systems with multiple energetically stable minima, vibrational states, localized in the wells, interact via tunneling. The interaction manifests itself in the energy shifts in the vibrational spectra. For symmetry-related minima, it results in the splittings of the otherwise degenerate minima. The size of the matrix elements that connect the states localized in different wells is highly sensitive to the height and shape of the potential energy barriers that separate them and can vary over many orders of magnitude even in a single system. The calculation of energy shifts and splittings using exact variational methods is therefore very demanding and limited to systems of only a few atoms.

Instanton theory provides a way to calculate these shifts at a much reduced computational cost in full dimensionality. It is based on determining the minimum action paths (MAP) that connect pairs of minima and evaluating the corresponding matrix elements semiclassically using a harmonic expansion of the potential around the MAP. We generalized the existing approach [1] to asymmetric tunneling paths and the wells that are asymmetric in energy or shape [2, 3].

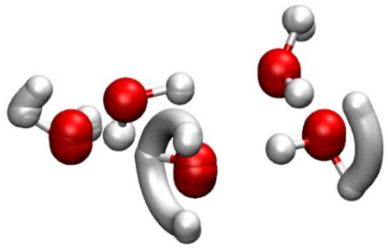

Figure 1. A tunneling rearrangement of the water pentamer: bifurcation accompanied by a flip.

We apply our approach to calculate the tunneling splitting patterns of some partially deuterated trimers [4] and the water pentamer [5] and interpret them in terms of feasible rearrangements of the clusters. In combination with the vibrational configuration interaction energies in a single well, we also calculate the vibrational spectrum of low-lying states in malonaldehyde [3] and obtain a good agreement with the exact MCTDH results [6].

References:

[1] (a) G. V. Mil'nikov, H. Nakamura, *J. Chem. Phys*. **115** (2001) 6881–6897; (b) G. V. Mil'nikov, H. Nakamura, *J. Chem. Phys*. **122** (2005) 124311.

[2] (a) M. Eraković, C. L. Vaillant, M. T. Cvitaš, *J. Chem. Phys*. **152** (2020) 084111; (b) M. Eraković, M. T. Cvitaš, *J. Chem. Phys*. **153** (2020) 134106.

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CL 1. Compound-Kinase Binding Affinity Prediction with Confidence Guarantees

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Machine learning efforts to advance drug discovery by simultaneously screening vast chemical spaces and learning from experimentally measured data have increased. Among the most popular targets of pharmacological interest is the human kinome where prediction of binding affinity is by definition a regression problem [1]. However, point predictions frequently appear oversimplified to accurately reflect the binding between a tested compound and a protein target, particularly when experimental data variation is considered. The utility of conformal prediction lies in this regard. Conformal prediction framework allows for the evaluation of individual point predictions and generates confidence estimates, as opposed to the conventional model performance evaluation over entire datasets [2].

Here we extend the inductive conformal prediction (ICP) framework for the compound-kinase binding affinity prediction problem in order to achieve prediction intervals that are more dependent on the input data (x) from the compound and target space and less dependent on the output values (y), thus complementing the applicability domain paradigm. In addition, we demonstrate that locating conformity regions for compounds and targets separately enables the retrieval of more meaningful calibration sets, resulting in higher validity and tighter prediction regions for new samples. We evaluate this approach on four distinct test sets with increasing difficulty levels (S1-S4).

References:

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[2] H. Papadopoulos, V. Vovk, A. Gammerman, *J. Artif. Intell. Res.* **40** (2011) 815–840.

CL 2. Evolution of Inhibition Models for Fluorinated *Cinchona* Alkaloids by Machine Learning

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Potential energy surfaces (PES) for 25 fluorinated *Cinchona* alkaloids derivatives were sampled by *ab initio* molecular dynamics [1] and used as independent variables in establishing activity/PES multivariate linear regression models (MLR) [2,3]. Principal components of previously measured inhibitory activities towards human acetyl- and butyrylcholinesterase were used as dependent variables.

An extensive machine learning protocol was applied for generating all possible MLR models with linear combinations of original variables as well as their higher-order polynomial terms. Evolution of regression model was monitored by calculation of R^2, adjusted and predicted R^2. Each regression model was fully validated by *leave-one-out cross-validation* (LOO-CV) and the best possible activity/PES models for different dimensionalities were selected based on R^2 values and the LOO-CV mean squared errors (Fig. 1).

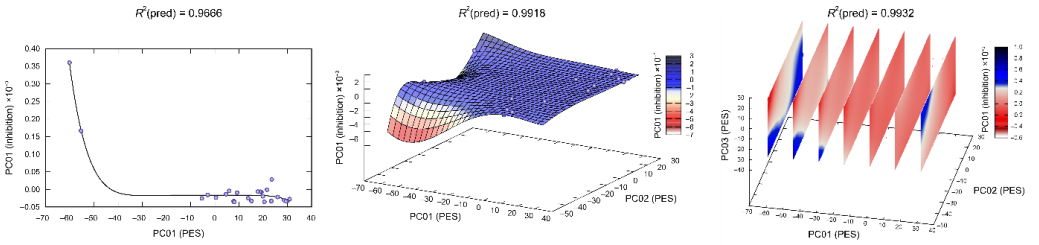

Figure 1. Progression of the best inhibition models for fluorinated *Cinchona* alkaloids derivatives depending on domain dimensionality.

Acknowledgments: This research was funded by the *Croatian Science Foundation*, grants: "Young researchers' career development - Training New Doctoral Students" (ESF-DOK-2018-09-3416) and "Activity and *in silico* guided design of bioactive small molecules" (IP-2016-06-3775). Research was using resources from Computational Center of Department of Chemistry, University of Zagreb Faculty of Science funded by European Regional Development Fund (infrastructural project CIuK, grant number KK.01.1.1.02.0016).

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[2] T. Hrenar, ***moonee***, *Code for Manipulation and Analysis of Multi- and Univariate Big Data*, rev. 0.68268, 2022.

[3] A. Matošević, A. Radman Kastelic, A. Mikelić, A. Zandona, M. Katalinić, I. Primožič, A. Bosak, T. Hrenar, *Pharmaceutics* **13** (2021) 420.

CL 3. Computational Chemistry Artillery Against Viruses

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The global COVID-19 pandemic mobilized both the scientific community and the pharmaceutical industry, and push them to rapidly design vaccines and new antiviral drugs. The drug discovery process is tedious and expensive. However, with introduction of machine learning algorithms and growth of computational power, high-throughput computing, and new, fast and reliable models with property predicting potentials became a pillar of the computer - aided drug design.

Deep neural network models predicting ligands' bioactivity against a variety of Flavivirus NS2B-NS3 proteases (including Dengue and Zika virus) were designed and validated. Primary structures alignment identified the NS2B-NS3 protease the most similar to the Kyasanur forest disease (KFD) virus protease, which helped us select the neural network model to be used in the drug repurposing study, and identify the compounds from Drug Bank database and Natural Product Atlas as the most potent KFD virus protease inhibitors. Molecular dynamics simulations and binding free energy calculations were used as additional and independent validation of our methods. Results obtained by machine learning, bioinformatics and molecular dynamics simulations reveal the most potent protease inhibitor as a new KFD virus' drug.

CL 4. Project HR-ZOO - The Final Stages of Implementation

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The main goal of the project Croatian scientific and educational cloud (HR-ZOO) is to build a national research and innovation e-infrastructure for the Croatian scientific and academic community. HR-ZOO infrastructure will provide a long-term advanced computing, storage and network resources as well as scientific software and specialized support to researchers that are necessary for multidisciplinary science and education. Advanced computing component consists of 1.1 PFLOPS high performance computing (HPC) resource, cloud computing resource with over 11,000 processor cores as well as virtual data centre infrastructure for deployment of critical services. Storage component will provide 10 PB of storage accessible via Network File System (NFS) or object storage S3 protocols. Resources will be deployed in five data centers connected with the new 100 Gbit/s network infrastructure.

In this presentation, we will describe HR-ZOO service catalogue with the emphasis on services that are most interesting to computational chemistry users. Furthermore, we will give an overview of the status of implementation of HR-ZOO infrastructure.

CL 5. Substituent Effect on Tunneling in Heterodimers of Benzoic Acids

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Carboxylic acid dimers possess at least two symmetry-related minima on their potential energy surface. These minima differ in the position of hydrogens in the carboxylic groups, and are separated with a finite potential energy barrier. The states in different minima interact via tunneling through the barrier, resulting in a double proton transfer. As a consequence, the energy of vibrational ground state splits into a doublet. The magnitude of the splitting is extremely sensitive to the shape and height of the potential energy barrier that separates the minima, making it a useful tool to probe the nature of the double hydrogen bond. We chose several heterodimers of *para*-substituted benzoic acids with substituents that display different electron-donating and electron-withdrawing properties and studied their impact on the proton tunneling.

The tunneling splitting is notoriously difficult to compute using exact quantum-mechanical methods. Instanton theory [1,2], on the other hand, is a semiclassical method that provides an approximate way to compute it efficiently. It is based on locating a minimum action path that connect the minima and calculating the wavefunction in its vicinity using a harmonic approximation. It is thus computationally inexpensive, treats the system in full dimensionality and provides an interpretation in terms of contributions of different vibrational modes to tunneling dynamics. This enabled us to compute tunneling splittings of several benzoic acid heterodimers using *ab initio* electronic structure calculations and to investigate the influence of substituents on different vibrational contributions. In order to confirm our results, we measured tunneling splittings in a selected set of heterodimers using chirped-pulse Fourier transform microwave spectroscopy, a high resolution spectroscopic technique.

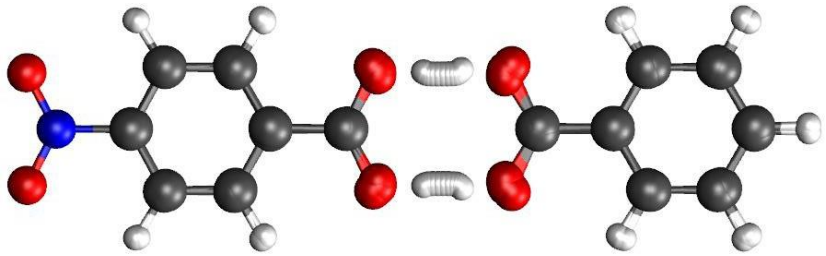

Figure 1. Minimum action path for the double proton transfer in the benzoic acid – nitrobenzoic acid heterodimer.

References:

[1] (a) M. Eraković, M. T. Cvitaš, *J. Chem. Phys*. **153** (2020) 134106; (b) ibid. **152** (2020) 084111.

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CL 6. Modelling Electron Spin Decoherence at Low Temperatures

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We present a method that predicts the decoherence of electron spins embedded in glass matrices under various refocusing spin echo pulse sequences in pulsed electron paramagnetic resonance experiments at low temperatures based solely on structural inputs [1]. Structural inputs of crystalline matrices are derived from crystallography data, while glass matrices are generated by molecular dynamics simulations. The electron spin decoherence profiles are solved from the structure inputs using the nuclear spin bath model and cluster correlation expansion method [2].

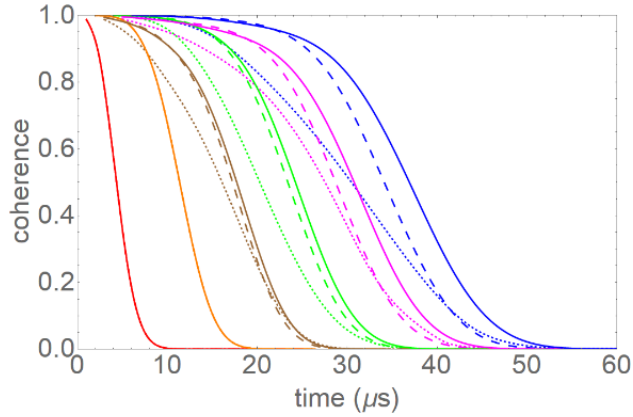

Figure 1. Calculated electron spin decoherence profiles of stable radical TEMPO in 1:1 (volume) frozen in glycerol/water matrix under dynamical decoupling pulse sequences with 1 (red), 2 (orange), 3 (brown), 4 (green), 5(purple), and 6 (blue) π-pulses, dotted lines: Carr-Purcell pulse sequences, dashed lines: Uhrig pulse sequences, solid line: numerically optimized dynamical decoupling pulse sequences [1(c)].

Our methodology produces good agreements with experimental results reported in the literature [3]. It also allowed optimization of inter-pulse delays of the multiple refocusing dynamical decoupling pulse sequences with up to six refocusing pulses [1(c)].

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CL 7. How Norvaline Affect the Stability of Secondary Protein Structures - a Computational Study

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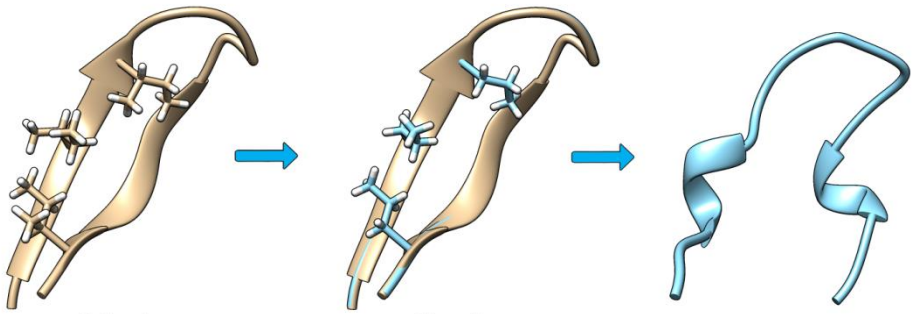
Norvaline is a straight-chain hydrophobic amino acid, not encoded by genetic code. It is of interest because of the industrial production of recombinant therapeutic proteins and peptides [1,2]. Namely, *E. coli* synthesizes norvaline in millimolar amounts under conditions of imperfect mixing in industrial bioreactors [3,4], which can then be incorporated into therapeutic proteins and peptides instead of leucine and isoleucine due to the erroneous activities of leucyl- and isoleucyl-tRNA synthetases [5,6]. Such mistranslated therapeutic proteins/peptides are considered to have non-native structures that are prone to aggregation and may even be toxic. To better understand the effect of norvaline on protein structure, we examined how norvaline affects the secondary protein structures using classical molecular dynamics simulations. The obtained results showed that norvaline has the highest destructive effect on the β-sheet structure compared to other analyzed amino acids and that the propensity of norvaline towards α-helix is the highest at elevated temperatures. These results explain the toxicity of norvaline and, additionally, indicate the potential beneficial contribution of norvaline in the design of thermostable proteins.



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CL 8. How to Interpret Trajectory Surface Hopping Dynamics?

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Trajectory surface hopping (TSH) dynamics is widely used to simulate nonadiabatic reaction dynamics and to investigate the mechanisms of photoinduced molecular processes [1,2]. However, it is often non-trivial to interpret the results of these simulations in the chemically intuitive way [3]. This is due to the fact that TSH dynamics is traditionally conducted in the basis of adiabatic electronic states, which, unlike the diabatic ones, tend to significantly change their electronic characters along the nonadiabatic reaction path.

In this work, an efficient protocol for the diabatization of electronic states along the surface-hopping trajectories will be presented. This includes the calculation of the surface-hopping diabatic populations and the decomposition of the time-resolved spectroscopic signals to the contributions of different diabatic transitions. The performance of the algorithm is illustrated for a number of prototypical photochemical systems.

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Posters

P 1. Understanding Binding and Hydrolysis of Neuropeptides in the Active Site of Human Dipeptidyl Peptidase III

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Dipeptidyl peptidase III (DPP III) is a dual-domain zinc exopeptidase that hydrolyzes dipeptides from the unsubstituted N-terminus of peptides of different sequence and size, with tetrapeptides to octapeptides being the best substrates [1]. There have been several attempts to explain the broad substrate specificity of DPP III [2-4] and to rationalize why some of the peptides are good substrates while the others are slow with high inhibition potency. We approached this problem computationally and derived possible explanations using various methods.

Using quantum molecular mechanics (QM/MM) calculations we determined the mechanism of the human DPP III catalyzed degradation of tynorphin (VVYPW) and Leu-enkephalin (YGGFL). Comparison of the enzymatic cycles determined for Leu-enkephalin and the slow substrate tynorphin gave us theoretical insight into the inhibitory mechanism of tynorphin. We found that tynorphin is cleaved by the same reaction mechanism determined for Leu-enkephalin [5]. More importantly, we have shown that the product stabilization and regeneration of the enzyme, but not nucleophilic attack of the catalytic water molecule and inversion at the nitrogen atom of the cleavable peptide bond, correspond to rate-determining steps of the overall catalytic cycle of the enzyme.

Complexes between human DPP III and neuropeptides experimentally identified as its ligands, either substrates or slow substrates, were subjected to micro second-long molecular dynamic (MD) simulations [6]. The simulations showed that good substrates were more suitable for hydrolysis due to the geometry of their position, the distances and angles between the scissile peptide bond and the E451 H-bound water molecule performing the nucleophilic attack in the reaction. In addition, MM/GBSA analysis indicated tighter and more specific binding of the peptide residues adjacent to the cleavable peptide bond with the highly conserved residues from the upper protein domain (H450 for Leu-enkephalin, and H450, H455 and E512 for hemorphin-4) during MD simulations.

This approach allowed us to obtain a wealth of data on the enzyme and to move one step closer to understanding its broad substrate specificity.

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P 2. Computational Study of the Monoamine Oxidase B Mechanism-Based Irreversible Inhibitors

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Monoamine oxidase B (MAO B) is a flavoenzyme responsible for the metabolism of endogenic and exogenic amines such as monoamine neurotransmitters whose disturbed homeostasis is implicated in the wide range of neurodegenerative pathogenesis. MAO B represents primary pharmacological target for the treatment of the Alzheimer's and Parkinson's disease. Commercial drugs, selegiline and rasagiline, are administrated with dietary restrictions and in high doses are associated with more frequent and greater intensity side effects [1]. There is a constant market pressure for the development of new, mechanism-based MAO B inhibitors with more favourable pharmacokinetic profiles.

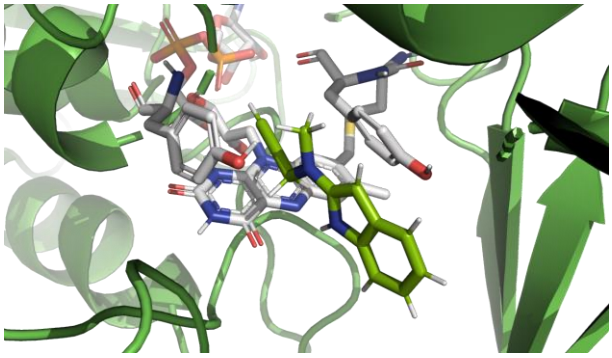

Figure 1. ,,Aromatic cage" of the MAO B active site with docked ligand.

MAO B active site is recognizable due to its ,,aromatic cage'' that consists of three aromatic components: two tyrosines and FAD (flavine adenine dinucletiode) cofactor [1]. Innovative approach was developed for the drug design which involves binding of the aromatic scaffolds [2] with propagylamine core which is present in commercial drugs which target MAO enzymes [3]. More favorable thermodynamic profiles are obtained using methods of script based molecular docking and molecular dynamics simulations. Quantum chemical cluster approach was used to acquire more optimal kinetic profiles of the inhibitory activity. Subsequent analysis indicated that new-designed molecules act in the accordance with the mechanism of the hydride abstraction mechanism, same mechanism that selegiline and rasagiline follow [3].

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P 3. Characterization of Diamondoid Ether Self-Assemblies on a HOPG Surface

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Diamondoids are polycyclic saturated hydrocarbons with diamond-like properties that can find application in various fields, especially as scaffolds in nanomaterial design [1]. Functionalization of diamondoids can give access to a plethora of useful derivatives and it is also possible to make diamondoid composites consisting of several diamondoid cage subunits connected with a heteroatom or a functional group. We recently prepared such composites that had an ether linker [2] in order to test their self-assembly capabilities on a material surface. More specifically, we deposited diamondoid ethers on a highly oriented pyrolytic graphite (HOPG) surface and used microscopy (STM) to identify the structural characteristics of the formed monolayers. Note that characterization of on-surface self-assemblies of such bulky cage molecules is challenging due to their non-planar nature. We also conducted a detailed computational analysis that revealed the most favorable on-surface orientations of these rigid molecules and confirmed that their spontaneous self-assembly was governed by London dispersion interactions acting between cage subunits. Moreover, we elucidated that the oxygen atom played an important role in directing the molecules towards the graphite surface (Figure 1), whereas the abundant side C–H contacts between the cages were crucial for the formation of an ordered 2D lattice. Thus, our findings provide one step forward in predicting on-surface behavior of non-aromatic organic compounds and their monolayer properties.

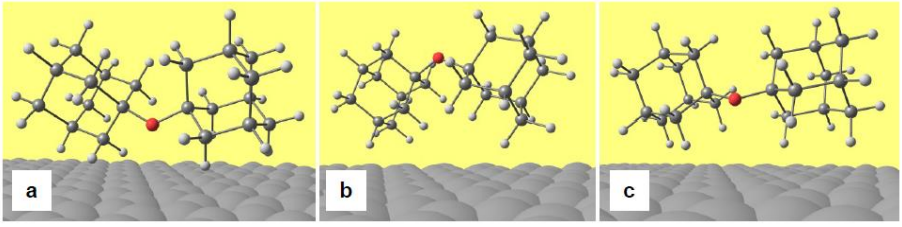

Figure 1. Feasible on-surface orientations of 1,1'-diadamantyl ether on graphite. Functional group directed, (a) towards the surface, (b) away from the surface, and (c) parallel to the surface.

References:

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P 4. DFT Study of Cysteine-Mediated *ortho*-Specific Deuteration of Azobenzene Using Cyclopalladated Azobenzenes as Precursors

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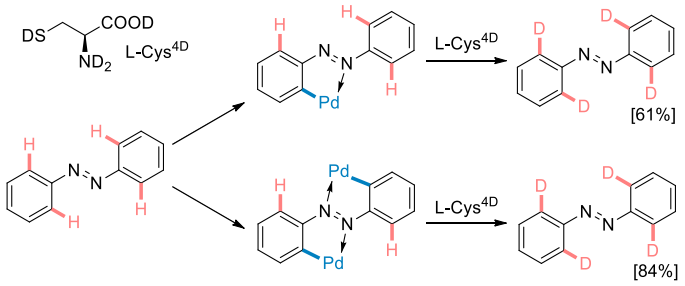
Acid-mediated hydrogen–deuterium exchange reactions (H/D exchange) are among the oldest methods known for labelling of aromatic compounds [1]. Nevertheless, site-selective high-degree deuteration of small molecules is still a complex procedure even though labelled substrates are in high demand [1]. Activation of the aromatic C–H bond by metal centers leads to cyclometalated complexes that in acidic environments can be converted back to the starting ligand [2]. If a deuterated acid is used, deuterium can be introduced to the ligand at the site of the metalation.

Recently our group prepared and studied a series of mono- and dicyclopalladated azobenzene complexes (Scheme 1) [3]. Experiments involving amino acid cysteine as a side ligand showed that this reaction leads to isolation of the azobenzene ligand. If a deuterated cysteine (Cys^{4D}) is used, site-specific deuteration at *ortho* position to the azo group of the ligand occurs.

Here we present the mechanistic DFT study of cleavage of the cyclopalladated complex by cysteine and formation of the *ortho*-deuterated azobenzene. Reaction involves formation of the cysteine cyclopalladated complex followed by a transfer of the deuteron from uncoordinated cysteine to the *ortho*-carbon atom.



Scheme 1

Acknowledgement: This work was funded by *Croatian Science Foundation* project IP-2019-04-9951 (MECHEMFUN).

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P 5. Impact of Positive Charge and Ring-Size on Interactions of Calixarenes with DNA, RNA and Nucleotides

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The influence of charge and size of calix[4] and calix[6]arenes to non-covalent interactions with DNA, RNA and nucleotides was investigated by combining several experimental and computational methods. We focused on calixarenes with very short, triazole-attached positively charged substituents and their neutral analogues. Cationic calixarenes have a red-shifted emission wavelength in comparison with neutral ones, due to smaller HOMO-LUMO energy gap. According to the TD-DFT/CAM-B3LYP calculations, HOMO and LUMO π-orbitals dominate the emission transitions for both neutral and cationic calixarenes.

Studied calixarenes bind nucleoside monophosphates with similar efficiency, by forming supramolecular complexes, with nucleobases inserted between aromatic pendant “arms” or “legs” grafted to calixarene rims (Figure 1.). Purine bases induce similar emission quenching of charged or neutral calixarenes, while pyrimidine bases induce a significantly stronger fluorescence quenching only for cationic calixarenes. A smaller pyrimidine base penetrates deeper into the calixarene cavity, than a purine base, influencing calixarene fluorophore properties more strongly [1]. Only cationic calixarenes non-covalently bind to ds-DNA and ds-RNA, by insertion into DNA minor groove and RNA major groove, with no changes in calixarene emission. Neutral calixarenes do not show any interaction towards DNA and RNA, but their Cu^{2+} complex fit into the grooves. Molecular dynamics simulations revealed that calixarene polynucleotide complexes are stabilized with electrostatic interactions of positively charged calixarene or metal complex and negatively charged phosphate backbones of the DNA/RNA.

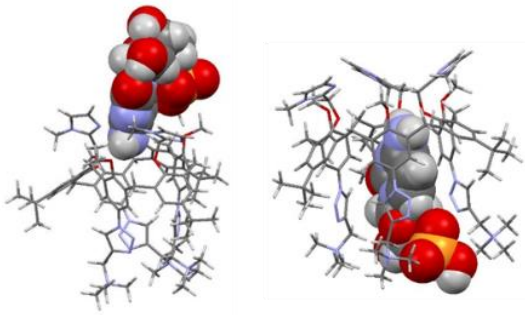

Figure 1. Complexes of calixarene (capped sticks style) with pyrimidine base (space fill) inserted between imidazoles (left) and triazoles (right), determined by molecular dynamics simulations

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P 6. Molecular Dynamics Study of the Interaction of Guanidinium and Ammonium Cations with Zwitterionic and Anionic Lipid Bilayers

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The mechanism of passage of cationic cell-penetrating peptides through phospholipid membranes is widely researched, but still unresolved question in biochemistry [1]. Arginine (Arg) -based peptides can pass through cellular membranes, while lysine (Lys) -based peptides cannot, though both amino acids possess the same +1 charge [2]. In order to provide molecular-level insight into the differing interactions of Arg and Lys with zwitterionic and anionic membranes, the model system was created using guanidinium (Gdm^+) and ammonium (NH_4^+) cations (Arg and Lys building blocks). Lipid bilayers consisting of 128 molecules of zwitterionic dipalmitoyl-phosphatidylcholine (DPPC) or anionic dipalmitoyl-phosphatidylserine (DPPS) were simulated in GROMACS, alone and with the addition of either NH_4^+ or Gdm^+ (0.1 M), NaCl as neutralizing salt, and 12800 water molecules. CHARMM36m force field was applied and the simulations were run for a total of 100 ns at two temperatures (above and below phase transition temperature of either lipid). The changes in membrane packing were evaluated by calculating properties such as area per lipid, membrane thickness and deuterium order parameters, while the interaction of cations was monitored through partial density profiles, radial distribution functions and quantification of cations adsorbed to the membrane. NH_4^+ and Gdm^+ both readily adsorb to the membranes and are located among the lipid headgroups, however Gdm^+ adsorbs in significantly higher amounts (50% more to DPPS and 100% more to DPPC), suggesting stronger physico-chemical interactions. Obtained results will be used to compare with experimental findings, in order to elucidate the different behavior of NH_4^+ and Gdm^+ with differently charged membrane systems.

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P 7. Anion-Induced Aza-Michael Addition of Furfurylguanidines to Dimethyl Acetylenedicarboxylate

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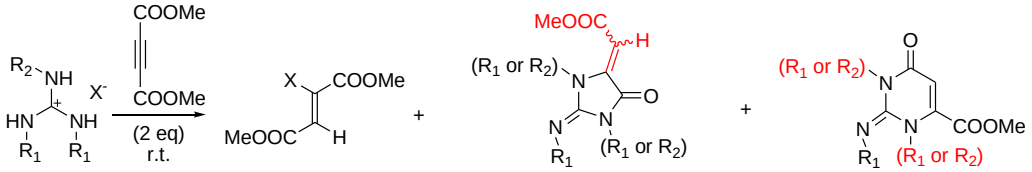
Cycloaddition of the furan derivatives to dimethyl acetylenedicarboxylate (DMAD) represents a highly atom-efficient approach to the oxanorbornadiene cage [1]. DMAD is highly reactive as a dienophile but also sensitive to the attack of nucleophiles like amines, thiols, neutral guanidines, etc [2]. Although guanidinium salts cannot be considered good nucleophiles, our preliminary investigations on the cycloaddition of guanidinium halides to DMAD indicated the formation of 2-aminoimidazolidin-4-one derivatives (aza-Michael reaction products) together with 2-halofumarate (Scheme 1).

Herein, we present results of the aza-Michael addition of furfurylguanidines to DMAD triggered by the addition of the anion to DMAD and subsequent deprotonation of the guanidinium cation. The mechanism for the process is proposed and investigated by DFT calculations. The structural diversity of the products is interpreted in terms of the stability of guanidine tautomers and/or sterical hindrance of the alkyl groups.



Scheme 1. General reaction scheme with the structural representation of the products isolated from the different reaction mixtures (X^- = Cl^- or I^-).

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P 8. What Can We Learn by Comparing Surface Hopping Algorithms?

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In order to study the dynamics of photochemical reactions that involve multiple excited electronic states, it is required to use methods beyond the Born-Oppenheimer approximation, i.e. nonadiabatic dynamics methods. Potential energy surfaces of multiple excited states are often complicated because there are many nonadiabatic regions where surfaces intersect or become very close in terms of energy. Therefore, the coupling between nuclear and electronic motion is no longer negligible. To simulate the dynamics of a system, the time-dependent Schrödinger equation must be solved. Obviously, this second order differential equation is very complex to solve exactly for any molecular system. Consequently, many different quantum and mixed classical-quantum methods for simulating nonadiabatic processes have been developed [1]. In this presentation the focus is on the Landau-Zener surface hopping algorithm which calculates the probabilities of an electronic state hop to occur, following the Landau-Zener formula. Since this method does not require calculating the nonadiabatic coupling terms, it could be very computationally effective. The Landau-Zener algorithm is put to the test using the molecule 4-*N*,*N*'-dimethylaminobenzonitrile as a well-studied model system. The obtained dynamics results are then compared with the results given by a few other nonadiabatic methods: Tully surface hopping, decoherence-corrected Tully surface hopping and the *ab initio* multiple spawning method [2, 3].

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P 9. HRP Protein – ABTS Substrate Orientation and Stability in Active Site

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In catalytic cycle of horseradish peroxidase (HRP) protein active site, hydrogen peroxide is decomposed to water and oxygen with high efficiency [1-4]. Poulos and Kraut proposed a stepwise acid-base process where hydrogen peroxidase and heme in coordination with histidine and neighborhood arginine form two key intermediates, compound 0 and compound I [5]. Crystal structures of redox intermediates (ground state and compounds I-III) are obtained using X-ray crystallography. ABTS substrate (2,2'-azinobis [3-ethylbenzothiazoline-6-sulfonic acid]-diammonium salt) is the most common substrate which is used for redox reaction of heme cofactor. Since heme group has complex intrinsic electronic structure and iron ion has different and complexed magnetic states, exact mechanism of ABTS with heme group is not completely known in literature even though it is well studied.

Investigation of catalytic reaction of HRP protein was performed using molecular dynamics (MD) simulations. Given the lack of a specific binding pocket, location of the best position and orientation of ABTS substrate at the active site of HRP protein is presented (Figure 1). The results of such studies are valuable to identify the optimal positions of the active site residues during the reaction. These findings could then be used to design the active site of the novel catalytic structure.

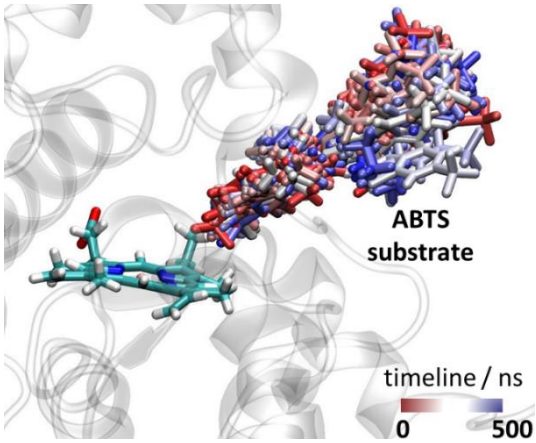

Figure 1. Aligned snapshots every 10 ns from trajectory for ABTS substrate in complex with active site of HRP protein.

References:

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P 10. Design of Azaazulene Derivatives as Inhibitors of Cholinesterases

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Cholinesterases play a fundamental role in regulating peripheral and central nervous systems. They are serine hydrolases containing a highly nucleophilic serine residue that participates in the catalytic triad (Ser-Glu-His) and are represented by two enzymes: acetylcholinesterase (AChE, E.C. 3.1.1.7) and butyrylcholinesterase (BChE, E.C. 3.1.1.8). The function of cholinesterases is to terminate the action of their natural substrate acetylcholine at nerve synapses. The irreversible inhibition of these enzymes leads to poisoning and can have fatal consequences. However, in neurodegenerative disorders such as Alzheimer's disease, acetylcholine levels in the brain decrease significantly over time, leading to dementia. The controlled moderate inhibition of cholinesterases slows down this process. Many compounds serving this role are isolated or designed, but the search for new therapeutic cholinesterase inhibitors is still very active.

Azulene, the isomer of naphthalene, is an aromatic molecule with one five- and one seven-membered ring. Azaazulenes are azulene analogs that contain one or more nitrogen atoms in one of the rings. We designed a set of 1-azaazulene derivatives and computationally investigated their inhibitory ability toward cholinesterases. Molecular docking was used to find the most favorable conformations of a complex between the tested molecule and the enzyme's active site. Visualizing the structures of complexes obtained by docking enabled the identification of interactions responsible for the accommodation of potential inhibitors into the enzyme active site. Analysis of docking results provided information on the influence of different molecule sizes, their conformational space, and substituent effects on their inhibitory activity.

Given that 1-azaazulene is a stable compound with established synthetic paths [1], these results can be used for further experimental testing of azaazulenes as cholinesterase inhibitors.

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P 11. Exploring Energy Surface of Gold Nanoclusters by Stochastic Search Method

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Over the years, stochastic search procedure for producing starting structures on the potential energy surface has evolved from 50 lines of Fortran code with simple and rugged idea, to a variety of different flavors and variants. We have developed some of them and implemented in a web-page variant [1]. The efficiency of our "kick" procedure was tested on the energy landscape of small gold clusters Au_n (n = 2, 4, 6, 8, 10). Most of the minima, reported earlier in benchmark studies, were easily reproduced. In all cases ($n \geq 4$) new configurations were discovered. A number of new minima located were calculated more stable than the previously reported structures. Some of clusters, reported in earlier studies, were not found by our "kick" procedure. This was due to nature of those stationary points. Instead of minima, they were saddle points with symmetry enforced optimization procedures.

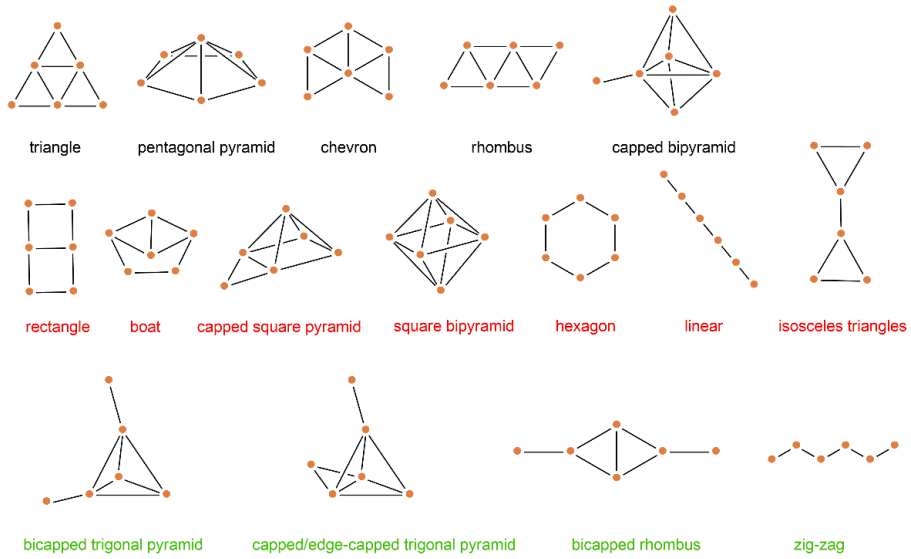

Figure 1. The first and second row: twelve different configurations of Au_6 cluster reported in the literature. Structures labeled in red color were not located by our kick procedure. New Au_6 cluster configurations located by a kick procedure in this work are labeled in green (• = Au atom)

References:

[1] Available at: https://kick.science, http://sw.pharma.hr/kick/, and https://github.com/DSakicLab/kick

P 12. Ferrocenoyl-Adenines: Substituent Effects on Regioselective Acylation

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A series of N^6-substituted adenine-ferrocene conjugates were prepared and the reaction mechanism underlying the synthesis was explored. The S_N2-like reaction between ferrocenoyl chloride and adenine anions is a regioselective process in which the product ratio (*N*7/*N*9-ferrocenoyl isomers) is governed by the steric property of the substituent at the N^6-position. Steric effects were evaluated by using Charton (empirical), Sterimol (computational), and SambVca $\%V_{Bur}$ (computational) parameters. Sterimol and SambVca parameters were calculated using new web-page implementation, with integrated Boltzmann averaging for conformer structures libraries [1]. The bulky substituents may shield the proximal *N*7 region of space, which prevents the approach of an electrophile towards the *N*7 atom. As a consequence, the formation of *N*7-isomer is kinetically less feasible process, i.e. the corresponding transition state structure increases in relative energy (compared to the formation of the *N*9-isomer). In cases where the steric hindrance is negligible, the electronic effect of the N^6-substituent is prevailing. That was supported by calculations of Fukui functions and molecular orbital coefficients. Both descriptors indicated that the *N*7 atom was more nucleophilic than its *N*9-counterpart in all adenine anion derivatives. We demonstrated that selected substituents may shift the acylation of purines from regioselective to regiospecific mode.

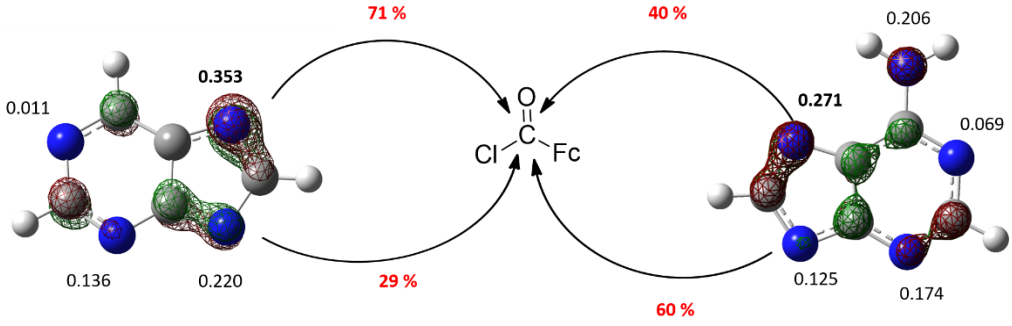

Figure 1. Relative yields (in red) of the regioselective reaction between purine (left)/adenine (right) and FcCOCl. HOMO coefficients (in black) calculated at the B3LYP/6-31+G(d) level (the largest value at the *N*7-atom is in bold).

References:

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P 13. Exact Wigner Function Evaluation for Different Basis Sets

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In this work we present closed-form expressions for different types of Gaussian integrals that occur when evaluating the Wigner function in a given basis. Wigner function represents a phase space distribution function from which positions and momentum can be, for example, sampled as initial conditions in molecular dynamics simulations. We focus on the harmonic oscillator basis and demonstrate the evaluation of the Wigner function. We also present results for the distributed Gaussian basis. Our results allow us to circumvents numerical evaluation and any imprecision associated to the procedure. Furthermore, our contribution is relevant beyond the scope of applications in quantum chemistry.

P 14. 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. Here 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 15. Theoretical Research Aimed at Achieving Regioselective Control within the Hofmann-Löffler-Freytag Reaction

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The Hofmann-Löffler-Freytag (HLF) reaction represents a distinctive radical-based procedure for the synthesis of nitrogen-containing heterocycles. Although the formation of piperidine and pyrrolidine rings is equally likely [1], due to the driving force being approximately the same, pyrrolidine rings are dominant product.

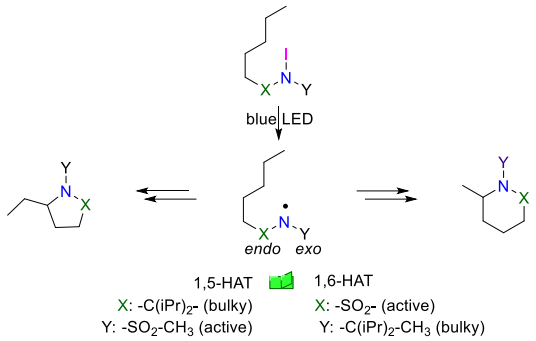

Figure 1. Interchanging bulky and activating group has the role of a mechanistic switch while guiding formation of the predominant product.

Finding a mechanistic switch that governs whether 1,5-HAT or 1,6-HAT reaction occurs is quite challenging. Possible candidates for a switch are presence/absence of steric bulk, presence/absence of chiral centers along the carbon chain, molecular flexibility and/or stereoelectronic effects. It has been shown that selective piperidine formation is plausible when C-H bonds at C_5 and C_6 carbon are equally reactive [2-4]. Placing a sulfoxide or sulfamide group at the C_2 position *endo* and a bulky group *exo* leads to the formation of piperidine product in predominant fashion as has been demonstrated by Short et al [3,4]. They have put forth an elucidation for predominant piperidine formation. Their reasoning is that elongated N-S and S-O bond and the compressed O-S-N angle geometrically favor seven-membered transition state, as in 1,6-HAT for the C-H abstraction [3,4]. Other works demonstrate predominant pyrrolidine products, although in almost all the cases C-H bonds at C_5 are more reactive as compared to C-H bonds at the C_6 position and the activating group is placed *exo*, with steric bulk having no significant influence on regioselectivity [5,6]. Here presented are calculated thermodynamical and kinetic parameters in our search whether positioning of activating and/or bulky groups in *exo* and *endo* position are the switch between pyrrolidine and piperidine products.

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P 16. Quantum Mechanical Docking of Small Bioactive Molecules within Cholinesterases' Active Sites

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The most important interactions of small molecules with cholinesterases were investigated by quantum mechanical docking [1]. A systematic search of the configurational space was conducted using a combinatorial search algorithm [2]. The following degrees of freedom were taken into account: three translational and three rotational degrees of freedom. Small molecules were translated within the active site in steps of 1 Å and rotated with increments of 60°. For every generated configuration electronic energy calculations were performed using the PM7 Hamiltonian and the search for all local minima was carried out [3]. For the selected local minima combined quantum mechanical/quantum mechanical (QM/QM) optimizations were performed and relative standard Gibbs energies of binding were calculated. All quantum chemical calculations were done using the Gaussian 16 program package.

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P 17. Visual Analytics of Structure-Activity Relationships of Natural Products and Drugs

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Natural products are a great source of novel molecules that can have beneficial effects on human health, not only as medicines, but also as nutrients and cosmetic ingredients. We have investigated compounds from the largest natural product database COCONUT, using data science and machine learning, and compared them with approved drugs from the ChEMBL database [1,2]. Among the various machine learning techniques, reducing the dimensionality of the multidimensional space for the purpose of visualization enables better understanding of large data sets. In the presented case study, we used advanced exploration and visualization tools to analyze structure-activity relationships (SAR) and reveal preliminary activities for subsets of natural products.

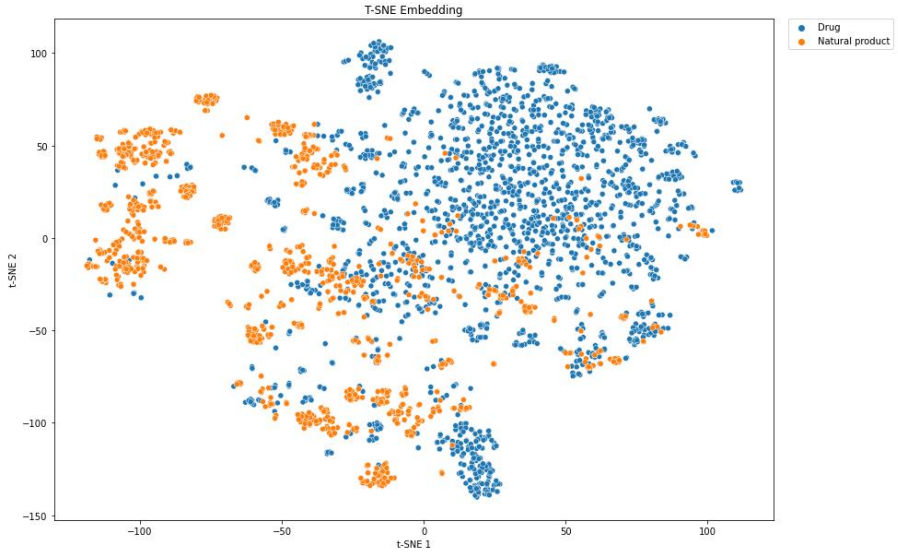

Figure 1. T-SNE embedding of chemical space of drugs and natural products from microalgae.

References:

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P 18. COVID-19 Infection and Neurodegeneration: A Potential Link Revealed by Computational Simulations

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Although COVID-19 has been primarily associated with pneumonia, recent data show that the SARS-CoV-2 virus can infect other vital organs, such as heart, kidneys and brain. The literature agrees that COVID-19 is likely to have long-term mental health effects on infected individuals, which signifies a need to understand the role of the virus in the pathophysiology of brain disorders that is currently unknown and widely debated [1]. Our docking and molecular dynamics simulations show that affinities of spike proteins from the wild type (WT) and South African (SA) variant for MAO enzymes are comparable to those for their ACE2 receptors [2]. This allows for the spike···MAO complex formation, which changes MAO affinities for its neurotransmitters, thus eventually impacting rates of their metabolic conversions and misbalancing their levels (Fig. 1). Knowing this fine regulation is strongly linked with the etiology of various neurodegenerative disorders, these results highlight the possibility that the interference with the brain MAO activity is responsible for the increased neurodegeneration following the COVID-19 infection. Since the obtained insight suggests a more contagious SA variant would produce even larger disturbances, and with new and more problematic strains likely emerging in the near future, we firmly advise that the demonstrated prospect for the SARS-CoV-2 induced neurological complications should not be ignored, rather requires further clinical investigation in order to achieve early diagnosis and timely treatment.

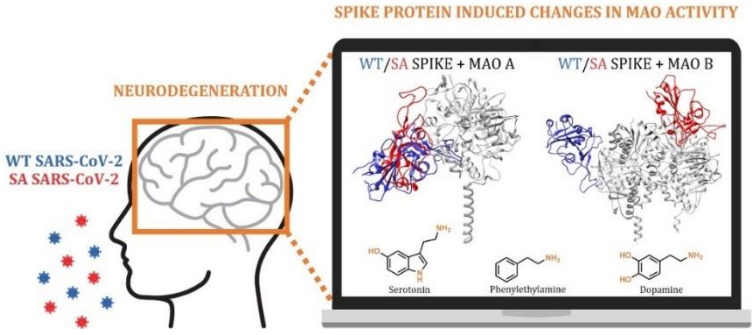

Figure 1. Schematic representation of the effect of spike proteins on the brain MAO activity.

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P 19. Neural Network Modelling of Potential Energy Surface of Methanoic Acid Spanned by Normal Coordinates

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Molecular dynamics and Monte Carlo calculations require a description of potential energy surface (PES) of an investigated system at arbitrary configurations. Accurate information at the higher levels of theory is computationally expensive to obtain and limited to a certain number of geometries. An ideal PES should have the accuracy of *ab initio* calculations and be as fast to evaluate as empirical or semiempirical models. As an alternative to standard interpolation methods for constructing PES from the results of first-principles energy calculations, several efforts to use artificial neural networks to describe PES have been reported [1,2].

In our study, we used reinforcement learning to train multilayer neural network, implemented in program ***moonee*** [3], for describing PES of methanoic acid spanned by normal coordinates. A particular strength of neural networks is that it can fit any real-valued, continuous function of *n*-dimensions to arbitrary accuracy using a finite number of parameters and it can effectively model data with noise. For all examined 1D and 2D PESs of methanoic acid, neural networks have shown that they can reproduce accurate description of investigated PESs using only a smaller number of total data points. The computational cost of training the neural network is small and we expect that this method will be useful in modeling a wide variety of PESs at the high level of theory for further molecular dynamics calculations.

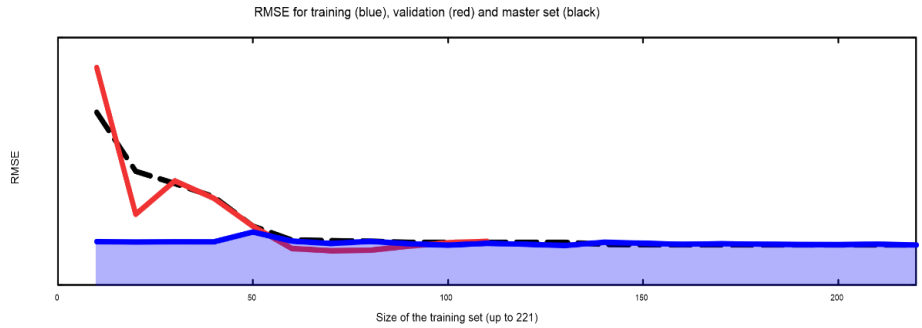

Figure 1. RMSE for 2D PES of methanoic acid spanned by two normal coordinates

Acknowledgments: This research was using resources from Computational Center of Department of Chemistry, University of Zagreb Faculty of Science funded by European Regional Development Fund (infrastructural project CIuK, grant number KK.01.1.1.02.0016).

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P 20. Enhanced Sampling of Nucleobase Assemblies in Water: Extracting Structural Motifs From Simulations

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The properties of molecular systems, such as aggregates in solutions or molecular crystals, are controlled by interactions between the molecular units. Optical properties are paradigmatic in this sense: the evolution of the optical responses from the isolated molecule to a supramolecular assembly and large crystal are directly connected to the interactions between the units, which in turn depends on the structural key feature of the soft matter [1].

As a first step in approaching this problem for biological molecules, we have focused on nucleobase assemblies in water. Besides being a good model system, nucleobases and their specific base pairing is the paradigm of molecular recognition in nature [2]. The hypothesis, in the context of prebiotic chemistry, focuses on the selection operated by nature, in terms of their structural properties, but also in respect of their stability under UV light. Modeling techniques can help in understanding the relationship between these elements from a fundamental and microscopic perspective.

For computational prediction of the structure of molecular assemblies, enhanced sampling techniques are ideally requested. In this work, we have explored the formation of N-mer nucleobase assemblies (N = 2 - 8) with classical potential, combined with well-tempered metadynamics. The AMBER99 RNA force field was reparametrized in order to avoid overestimation of stacking interaction [3]. We have employed both: a) a combination of 2 collective variables defined as contact numbers for pi-stacking and Watson-Crick hydrogen bonding interactions; b) a newly developed geometrical descriptor based on distance and orientation of molecular pairs.

Acknowledgments: The research was supported by Croatian Science Foundation (“Hybrid modeling for excited states in novel molecular materials: from optical properties to exciton dynamics”, HYMO4EXNOMOMA, IP-2020-02-7262).

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P 21. Predicting the Structure of Quasi-Two Dimensional Lead-Halide Perovskites

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Hybrid quasi-two-dimensional perovskites (Q2DPs) are a class of materials consisting of lead-halide perovskite slabs intercalated with (bi)layers of organic cations. The rich variety of possible chemical compositions of Q2DPs allows for their characteristic wide tunability of photophysical properties.

We present a structure prediction method, dubbed GO-MHALP (Global Optimization by Minima Hopping Algorithm for Layered Perovskites), which intends to predict the detailed crystal structure of a Q2DP of a given chemical composition. GO-MHALP is a minima hopping algorithm that utilizes transferable classical potentials for energy and force evaluations. It features an on-the-fly method for detailed exploration of local PES basins. Accurate structures are obtained by a single DFT relaxation of the found global minimum.

We employ GO-MHALP in a joint experimental and computational investigation to show that specific ordering of iodine and bromide halides in the inorganic lattice allows for the stabilization of a Q2DP containing the bulky tert-butyl ammonium cation.

P 22. Structural Determination of $[Zn(L)_2]^{2+}$ Complex (L = Acetamide-Pyridine Ligand) from Liquid NMR Measurements and DFT Computations

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Asymmetric tridentate ligands **L** (L= acetamide-pyridine) of the type A-B-C, (Figure 1a) enrich the isomerism of *bis*-tridentate A-B-A ligands [1] to six possible isomers of $[M(A\text{-}B\text{-}C)_2]$ complexes (M=metal, Figure 1b). Ligand **L** and metal complex $\mathbf{[Zn(L)_2](BF_4)_2}$ have been synthesized and characterized by solution-state NMR (^{1}H and ^{13}C). It is generally known that ligand coordination to the metal atom destroys NMR magnetic equivalences of nuclei near the metal atom, therefore increasing the number of signals in NMR spectra and appearance of hidden *J*-couplings (Figure 1c). Magnetic equivalences originate from fast nuclei-exchange processes (faster than NMR timescale), due to rotational/inversion motions of molecules in solution. Therefore, the DFT simulation of solution-state NMR spectra is a computational challenge and only recently satisfactory procedures have been suggested [2]. Herein, the conformational space of ligand **L** and complex $\mathbf{[Zn(L)_2]^{2+}}$ has been explored by the CREST program [3]. Ensembles of conformations were optimized on the DFT theory level and free energies were calculated. For conformers with Boltzmann population > 1% the NMR parameters (shifts and *J*-couplings) have been calculated by the DFT/GIAO theory using the ORCA program [4]. Finally, from differences between measured and calculated NMR data, the most probable isomer of $[Zn(L)_2]^{2+}$ complex in solution is obtained.

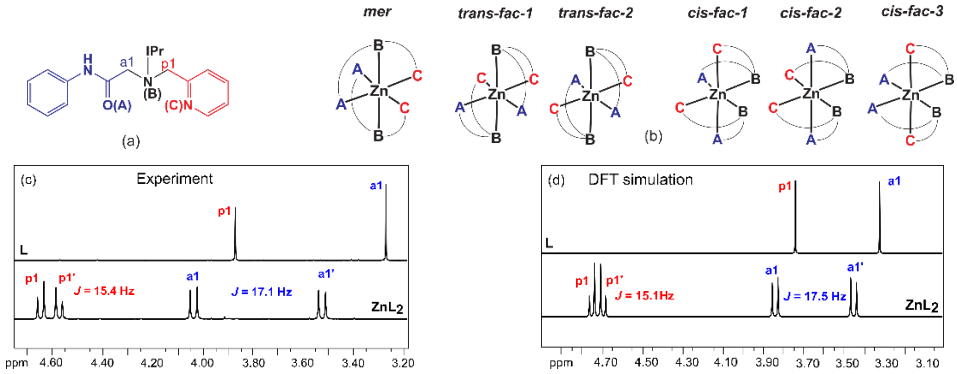

Figure 1. Ligand **L** (a), $\mathbf{[ZnL_2]^{2+}}$ isomers (b), CH_2 region of ^{1}H NMR experimental (c) and simulated (d) spectra.

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P 23. Message Passing Neural Network Potentials for Molecular Crystals

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In this work, we investigate the application and limitations of message passing neural networks (MPNNs) on a molecular crystal (MC). Used MC system has interesting thermal expansion properties useful for gauging the predictive properties of MPNNs trained on energies and forces.

The dataset is created using normal mode sampling of three structures representing the phases of the MC. The synthetic data for the dataset is created using DFT in VASP at the R2SCAN level.

Two different MPNNs, SchNet and NequIP, were used. The difference in their architecture and the impact of different hyperparameters on prediction energy and forces were investigated. Additionally, we looked at the applicability of transfer learning on SchNet and active learning on NequIP for improving the accuracy and predictiveness.

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

P 24. Extending Non-Equilibrium Pulling Method in GROMACS with Arbitrary User-Defined Atom Weight Factor Expressions

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Numerous non-equilibrium methods are used in modern molecular dynamics simulations. Specifically, non-equilibrium pulling can be used to simulate protein unfolding, ligand unbinding, and uniform flow as well as perform umbrella sampling. Recently, GROningen MAchine for Chemical Simulations (GROMACS), a popular molecular dynamics simulation software package, introduced a transformation pull coordinate that allows arbitrary mathematical transformations of pull coordinates. This enables changing the pull direction, rate, and force during the simulation in a user-defined way. While these are generally useful, performing uniform flow simulation, as shown in Figure 1 and described in [1], requires changing the force applied to the atoms of the pull group during the simulation. The extension of GROMACS we developed offers the ability to specify an arbitrary user-defined atom weight factor expression. This approach, in particular, allows specifying the hard-coded smooth or non-smooth weighting of the pull group used in [1] and presented in Figure 1. While the weighting could previously be derived only from the position in the x coordinate, the generalized approach additionally allows the positions in y and z coordinates as well as the velocities in all three coordinates to be used in the weight factor expression. The implementation is publicly available on GitLab and will be submitted for inclusion in a future version of GROMACS.

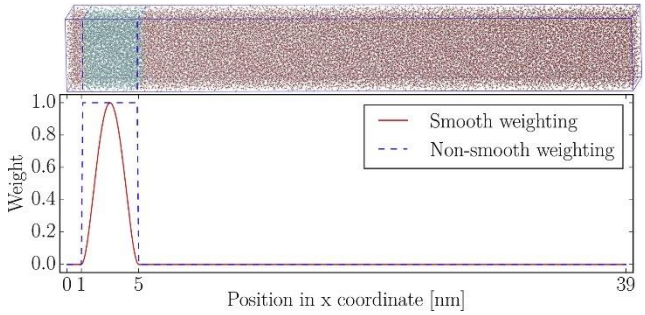

Figure 1. Example setup for flow MD simulations (taken from [1]). The arbitrary user-defined atom weight factor expressions enable weighting as shown, among many others.

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P 25. A DFT-Based Method Suitable for Calculating Hot Carrier Energy Distribution in Alloys

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Upon excitation with light, collective oscillations of electrons (called plasmons) can be induced in a metal nanoparticle. Plasmon decay leads to generation of "hot" charge carriers of extremely high energy. Alloying has recently been explored by density functional theory (DFT) for plasmonic properties tuning [1], but the effect of alloying on hot carrier generation so far remains unexplored.

On the one hand, the rigorous methods for calculating hot carrier distribution are very seldomly used due to their complexity. On the other hand, the most popular method, based on simple density of states (DOS) calculation, is overly approximative and is not able to identify the main differences between hot carrier distribution in alloys and pure metals. Therefore, there is a need for a more rigorous computational method, but simple enough to find wide acceptance and use in the field.

In this work, we present a relatively simple method based on joint density of states (JDOS) which can be easily interfaced with an existing DFT code (GPAW). Furthermore, we compare it to the popular DOS-based method and show that our approach properly identifies some of the key differences between hot carrier energy distribution in alloys and pure metals. Finally, we explore alloying as a way of tuning the hot carrier energy distribution and the implications of the results for practical applications.

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P 26. Computational Analysis of the Stereochemistry of ML_2 Metal Complexes with Bpa and Imda Ligands

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Bis-tridentate metal complexes of flexible ligands can form three different geometric isomers: *mer*, *trans-fac* and *cis-fac* [1]. The stability of isomers is influenced by many factors such as electronic and steric properties of the coordinating ligand, type of metal ion, possibility of forming non-covalent interactions, type of anion present and others. Understanding the isomer preferences in those systems is an important starting point in the development of new complex compounds with desired form and properties [2,3].

In this work, derivatives of tridentate ligands bis(pyridine-2-ylmethyl)amine (bpa) and 2,2'-iminodiacetamide (imda) were prepared, as well as their corresponding complexes with different Zn(II), Cu(II), Ni(II) and Co(II) salts. Oxygen and sulfur, as well as -NPh- and -PPh- functional groups were chosen as central donor atoms. The solid-state structures of prepared complexes were characterized by single-crystal X-ray diffraction, while the structures in solution were studied by NMR spectroscopy. The stoichiometry and the stereochemistry of these complexes, together with possible conformations of their substituents, were studied using the (SMD)/M05-2X/6-31+G(d) DTF computational approach to determine their relative stability. Experimental and computational results were compared and preferences of some central donor atoms to form specific isomers of ML_2 complexes were observed. One of our goals was to determine which factors lead to formation of *cis-fac* isomers, which could, in the case of nitrogen or phosphorus as central atoms, be used in the development of new selective catalysts.

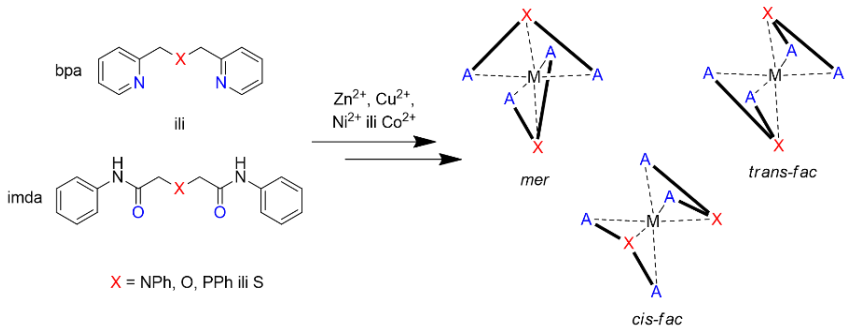

Figure 1. ML_2 complexes of flexible bpa and imda ligands, M = Zn^{2+}, Cu^{2+}, Ni^{2+} i Co^{2+}.

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P 27. Adsorption of Neonicotinoids and Their Degradation Products on Carbon Nanomaterials

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The extensive use of pesticides in areas such as agriculture and public health has resulted in this class of compounds becoming a widespread pollutant. Currently, most wastewater treatment plants are ineffective in the removal of pesticides and other micropollutants [1]. Taking into consideration trends of increasing pesticide use, the issue of pesticide pollution is only expected to worsen, leading to increased efforts in the search for an efficient means of their removal from natural environments. Adsorption onto carbon nanomaterials, an easily implementable process able to remove pesticide pollutants, has received much attention [2].

In recent decades, neonicotinoids, the most commonly used class of insecticides, have come to attention due to their negative impact on honey-bee populations. Now, neonicotinoids are on European Union Watch List of contaminants of emerging concern. However, given the frequency of detection of neonicotinoid mixtures [3] and their tendency to undergo degradation, there is a scarcity of studies on the adsorption of neonicotinoids and their transformation products.

In this work, we use density functional theory to explore the thermodynamics of adsorption of five neonicotinoids and nineteen of their transformation products on four different carbon nanomaterials (graphene, graphene oxide, semiconducting and superconducting carbon nanotubes) at environmental pH, in water and n-octanol. We examine the differences that result from various modes of neonicotinoid degradation, as well as how such changes influence the balance of forces contributing to the overall adsorption mechanism. We also investigate the differences in pollutant adsorption to carbon nanotubes of differing chirality.

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P 28. High Performance Computation as a New Frontier in Studies of Supramolecular Organization and Substrate Channeling in Cell Physiology and Disease Development

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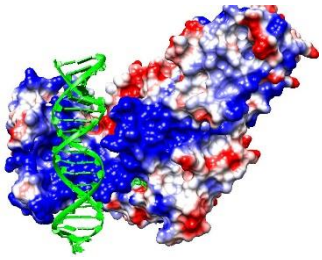
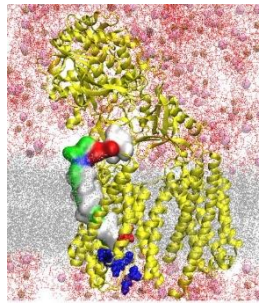
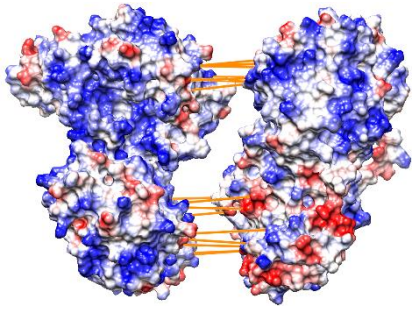


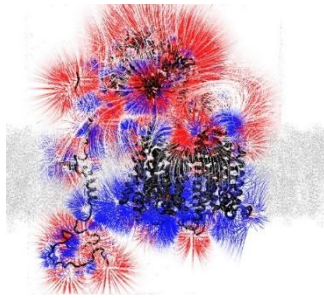
Human DNA methyltransferase Dnmt1: development of drugs for epigenetic regulation



Intramembrane protease γ-secretase: enzymology inside cholesterol-lipid-bilayer



H-bonds in LDH-GAPDH supramolecular complex: NAD(H) channeling in anaerobic glycolysis



Protein-aggregation in biological membranes: molecular foundations of Alzheimer disease

We are using high-performance computation as a molecular microscope that can describe how thousands of molecules can form supramolecular structures in cells. Supramolecular organization can describe at the molecular level how chemistry forms life, and cell physiology and disease development. We will describe how supramolecular organization can control metabolic regulation by substrate channeling. We show how to produce drugs that can control the functional organization of the human genome epigenetics. Epigenetic regulation is defined as the greatest challenge for the pharmaceutical industry in the 21st century. We describe how the aggregation of the sticky protein junk can lead to Alzheimer's disease and why this disease represents the new medicine in the 21st century.

P 29. Design and Development of Novel pH-Sensors Based on Iminocoumarin Derived Imidazo[4,5-*b*]pyridines

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Design and development of molecules for (chemo)sensing and optoelectronic applications is of great interest in organic chemistry and sensing technology [1]. Benzazoles are among the most privileged heterocyclic subunits in the medicinal chemistry due to a wide range of bioactivities [2], while iminocoumarins are known for interesting spectroscopic features. It is no surprise that their conjugates are being explored for pH sensing applications based on their excellent spectroscopic response in correlation with pH value [3]. Here we present the synthesis and spectroscopic characterization of novel iminocoumarin derived imidazo[4,5-*b*]pyridines in several polar and non-polar solvents (Figure 1). The absorption spectra reveal a strong dependence on iminocoumarin substituents, solvent polarity and pH, which allows a potential use as sensitive and selective optical sensors in biological, environmental, and chemical processes [4].

To determine their precise protonation state under different pH conditions, we calculated the matching pK_a values with the (SMD)/B3LYP/6-31+G(d) model. The results are in very good agreement with experiments, and reveal that under neutral pH = 7, these systems are present as cations monoprotonated at the *exo*-imine, while in the pH range 1–13, they exchange between neutral and diprotonated forms, which is responsible for alterations in UV-Vis responses.

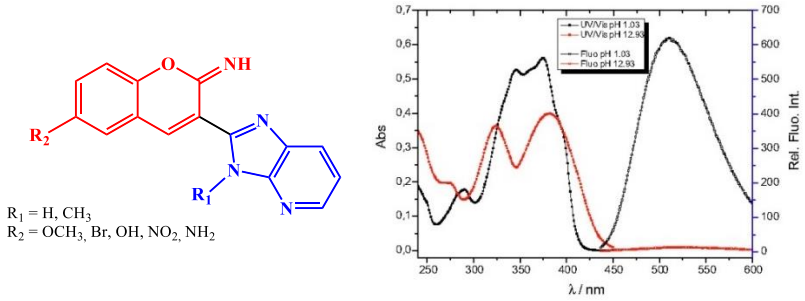

Figure 1. Chemical structures of potential pH sensors (left), and a typical absorption and fluorescence emission spectra (R_1 = H, R_2 = OCH_3, λ_{exc} = 380 nm) at pH = 1.03 and pH = 12.93 (right).

Acknowledgments: This work was funded by the Croatian Science Foundation (project number HRZZ-8090 BenzpHSens).

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Notes

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