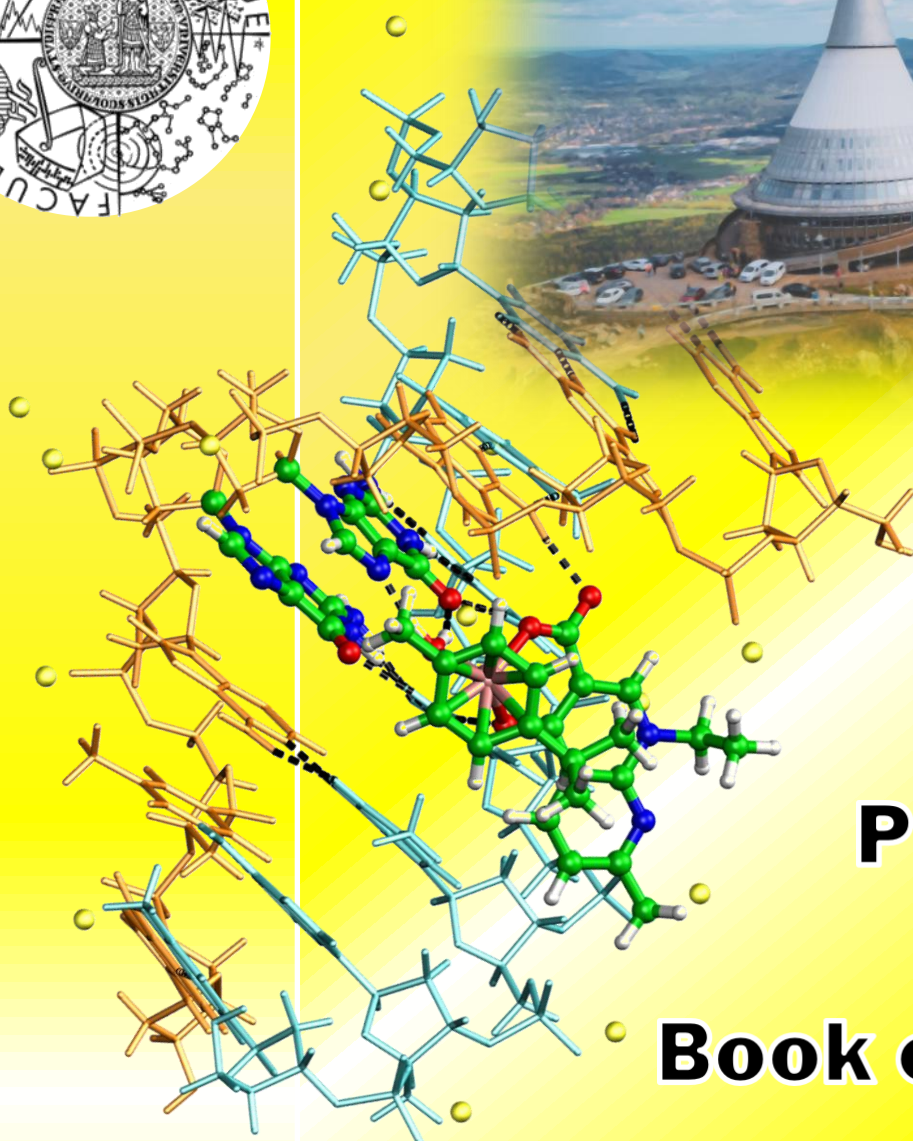


Modeling Interactions in Biomolecules X

Liberec, 6th – 10th September 2026



**Program
&
Book of Abstracts**

Modeling Interactions in Biomolecules X

Liberec, Sep 6-10 2026, Czech Republic



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Liberec

Liberec is the regional capital of North Bohemia and the fifth-largest city in the Czech Republic, home to over 100,000 residents. Nestled in a picturesque valley between the Ještěd Ridge and the Jizera Mountains, the city enjoys a strategic tri-border location just a short drive from both Germany and Poland. This geographic position has historically shaped Liberec into an essential crossroads for Central European trade, cross-border culture, and mountain tourism.

First mentioned in historical records in 1352, Liberec developed steadily through trade and artisanal weaving. The city's golden age arrived in the 19th and early 20th centuries with the Industrial Revolution. Spearheaded by prominent industrialists like the Liebig family, Liberec became the epicenter of the Austro-Hungarian textile and manufacturing industries. The sheer volume of its wool and cloth production earned it the moniker "the Manchester of Bohemia", which in turn financed grand urban developments, opulent residential villas, and modern infrastructure.

In the post-industrial era, Liberec successfully pivoted from traditional mechanical weaving to high-tech research and cutting-edge engineering, centered around the Technical University of Liberec (TUL). Founded in 1953 as a textile engineering institute, the university remains a global leader in material science. The university's most celebrated breakthrough is the Nanospider™ technology—developed by TUL research teams led by Professor Oldřich Jirsák in close collaboration with the Liberec-based company Elmarco. Nanospider is a patented, needle-free electrospinning process that produces nanofibers on an industrial scale using high electrostatic voltage. As the world's first commercially viable method for high-volume nanofiber production, it cemented Liberec's reputation not just as a city of historic textiles, but as a global pioneer in advanced nanotechnology, modern medicine, and filtration materials.

Liberec's built environment reflects its rich, multifaceted history:

- *Liberec Town Hall*: Completed in 1893 by Viennese architect Franz Neumann, this grand Neo-Renaissance landmark closely resembles the Vienna City Hall, standing as a symbol of the city's civic pride.
- *Liberec Chateau*: A historic noble residence, built in the Renaissance style, was completed in 1587 by the Redern family. The rare Renaissance chapel from the beginning of the 17th century has been preserved in the chateau. While its historic exterior and surrounding areas are key city landmarks, full interior public access is limited.



Main Square



Chateau



Šolc's House

- *Waldstein Houses*: A preserved cluster of 17th-century half-timbered houses offering a rare glimpse into the town's pre-industrial appearance.
- *Šolc's House*: A beautifully preserved 1771 half-timbered building that stands as a rare surviving example of traditional Upper Lusatian architecture in Liberec. Originally built for a local cloth maker, this historic timber-framed landmark now serves as a cultural site and gallery showcasing the region's 18th-century artisan heritage.
- *Ještěd Tower*: Rising 1,012 meters above sea level atop Mount Ještěd, this hyper-modernist, cone-shaped hotel and television transmitter designed by Karel Hubáček won the prestigious Perret Prize and remains the region's defining skyline feature. A tour is scheduled there for Tuesday.
- *Liberec Zoo and Botanical Gardens*: Founded in 1904, the Liberec Zoo is the oldest zoological garden in the former Czechoslovakia, globally renowned for its conservation projects and historical breeding of rare white Bengal tigers. It sits directly adjacent to one of Central Europe's most species-rich botanical gardens.
- *Babylon Centrum*: The largest indoor amusement park in the Czech Republic including a beautiful aquapark with its steampunk-style décor.



Ještěd Tower



White tiger in the Zoo



Aquapark

Scientific program

Tuesday

Wednesday

Thursday

Sunday

14:00–16:00	Registration	
chairlady	<i>J. S. Murray</i>	
16:00–16:15		Conference opening
16:15–17:05	W. Jorgensen	Evolution of Computer-Aided Drug Discovery
17:05–17:55	F. J. Luque	Ligand-Protein Hydrophobic Complementarity: Application to the Design of Antiviral Compounds
19:00–21:00	Welcome party	

Monday

chairman	<i>W. Jorgensen</i>	
9:00–9:30	D. Salahub	Exploring Quantum Algorithms for Machine Learning and Quantum Chemistry on Quantum Computers
9:30–10:00	R. Szabla	Machine Learning Potentials for Chemistry and Dynamics of RNA and DNA
10:00–10:30	J. Pittner	Accelerated Surface Hopping MD via Scaling of Spin-Orbit Couplings: Opportunities for Machine Learning and Applications
	Coffee break	
chairman	<i>N. Gresh</i>	
11:00–11:30	R. Friedman	Multivalent Metal Ions, Proteins and Drugs
11:30–12:00	M. Mitoraj	Theoretical Description of Hydride-Hydride Interactions in Selected Hydrogen Storage Materials
12:00–12:30	M. Straka	Solvation, Aggregation, and the Predictive Power of ^{109}Ag NMR Calculations in Silver–Carborane Systems
	Lunch	

chairlady	<i>G. Mazzone</i>	
14:00–14:30	J. Murray	Revisiting “Intuitive” and “Counter-intuitive” Interactions: New Insights
14:30–15:00	S. Zarić	Oxidation-State-to-Coordination-Number Ratio Predictor of Hydrogen Bonding Strength in the Second Coordination Sphere of Metal Complexes
15:00–15:30	P. Kędzierski	Use of Static and Dynamic Catalytic Fields to Validate Alternative Enzyme Reaction Mechanisms and Explain the Catalytic Role of Zero-Point Vibrations
15:30–15:35	Conference photo	
	Coffee break	
15:50–17:20	Poster session	
	Dinner	

Tuesday

chairman	<i>D. Salahub</i>	
9:00–9:30	P. Paneth	Mechanisms of F ₄₃₀ -Catalyzed Dehalogenations Revealed by Theoretical Calculations
9:30–10:00	H. dos Santos	Exploring the Myostatin Activation Pathway: A Promising Target for Treating Muscle Atrophy
10:00–10:30	C. Adamo	Noncovalent Weak Interactions with DFT: From Molecules to Biogenetic Crystals
	Coffee break	
chairman	<i>P. Bouř</i>	
11:00–11:30	L. Chomicz-Mańka	How Does Microhydration Affect the Dissociative Electron Attachment? MD, QM and Experimental CEMB Studies on 8-(trifluoromethyl)thioadenine in Water Clusters
11:30–12:00	Z. Futera	Approximate Electronic-Structure Methods for Charge Transport in Biomolecular Junctions
12:00–12:30	G. N. Jonnalagadda	Charge Transport on Heterogenous Bio/Metallic Interfaces
	Lunch	
14:00–19:00	Sightseeing tour	

Wednesday

chairman *C. Adamo*

9:00–9:30 [V. Moliner](#) Computational Studies of Enzyme Catalysis: Toward the Design of Novel Therapeutics

9:30–10:00 [K. Świderek](#) Decoding Enzymatic Plastic Degradation: Computational Insights into Polyurethane Upcycling

10:00–10:30 [G. Mazzone](#) Light in Medical Treatments: Mechanistic Insights from Computations

Coffee break

chairman *V. Moliner*

11:00–11:30 [P. Kulhánek](#) Enthalpy/Entropy Decomposition in PMF Simulations

11:30–12:00 [E. Dyguda-Kazimierowicz](#) Biomolecular Recognition via the MED Model: From First-Principles Scoring to Broader Biophysical Applications

12:00–12:30 [P. Jurečka](#) QM-Derived Empirical Force Fields Improve DNA and Protein–DNA Simulations

Lunch

chairman *P. Paneth*

14:00–14:30 [A. Stachowicz-Kuśnierz](#) Molecular Dynamics Studies of the Interactions Between Bacterial Cell Envelopes and Products of Plastic Degradation

14:30–15:00 [J. Korchowiec](#) Evolution of Charge Sensitivities During MD Simulations

15:00–15:30 [N. Gresh](#) Asset of Separability for QC-Inspired Polarizable Intermolecular Potentials

Coffee break

chairman *T. Wesolowski*

15:50–16:20 [S. Yourdkhani](#) Probing Pseudopotential Artifacts Through the Lens of Non-Covalent Interactions

16:20–16:50 [P. Bouř](#) Computational Approaches for Raman Optical Activity

16:50–17:20 [M. Szkandera](#) Uncovering Solar Panel Defects with an EPR Probe

Dinner

Thursday

chairlady *S. Zarić*

9:00–9:30 [A. Michalak](#) Estimation of Charge-Transfer Excitation Energies from Energy Decomposition Analysis

9:30–10:00 [O. Żurowska](#) Combining Deformation of Molecular Electrostatic Potential with NOCV Orbitals: The Δ MEP-NOCV Approach

10:00–10:30 [D. Berta](#) Accelerating Quantum Embedding for Accurate QM/MM Calculations

Coffee break

chairman *A. Michalak*

11:00–11:30 [M. Srnec](#) Thermodynamic principles behind H-atom abstraction mechanisms and reactivities

11:30–12:00 [T. Wesolowski](#) FDET eigenvalue equations for a new class of applications

12:00–12:30 Concluding remarks

Poster presentations

Poster no.	Author name	Poster title
1	L. Gibala	Influence of Water Models on Protein–DNA Interactions: A Comparative Study
2	J. Novotný	Structure Analysis of Ternary Complex of Pt(II) Metallodrugs and Cucurbituril CB[8]
3	H. Padmanaban	Comparing RESP-Based Approaches for Deriving Partial Charges in Biomolecules
4	J. Pavolko	Combined QM/MM Description of Electron Transfer Between Coenzyme FAD and diCys Redox Center of TrxR
5	M. Pocheć	Machine Learning in RNA Atomistic Simulations
6	M. Pospíšil	Paracetamol Adsorbed into Metal Organic Framework MIL-140C
7	F. Šebesta	Modeling Host-Guest Interactions of B ₁₈ H ₂₂ and Cyclohexane in MOFs Using the Hybrid QM/MM Approach
8	B. Tomyšlak	A-type Helicity Controls Efficient Nonenzymatic Template Copying of Nucleic Acids
9	V. Volko	Pseudocontact NMR Shifts in Transition-Metal Compounds and Their Supramolecular Complexes
10	J. Vysloužilová	Simulation of Electron Transfer on Biomolecular Bridges by Non-Adiabatic Molecular Dynamics
11	F. Włodek	Interactions of Ultra-Fine Polystyrene Nanoparticles with Lung Surfactant Monolayers and Bilayers: A Combined Molecular Dynamics and Experimental Study.
12	J. Zdráhala	Calculating resonance Raman optical activity for transition metal complexes: importance of explicit solvation
13	J. Zemaník	Computational and QM/MM Study of Galactofuranosyltransferase GlfT1 of <i>Mycobacterium tuberculosis</i>
14	M. Zgarbová	Evaluation of DNA Force Fields: A/B Conformational Equilibria, Sugar Puckering, and Water Model Effects

Talk Abstracts

Evolution of Computer-Aided Drug Discovery

William L. Jorgensen

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Over the last thirty years, computer modeling has evolved into an essential, widespread activity in drug discovery. The contributions of our group have been in multiple areas including virtual screening, prediction of ADME properties, and FEP-guided lead optimization. The advances were all accompanied by development of new software including the BOMB program for *de novo* design, QikProp for AI-based estimation of pharmacological properties and metabolites, and MCPRO for Monte Carlo simulations of protein-ligand complexes. To pursue prospective studies, our efforts were expanded to include synthesis, biological assaying, and crystallography. Emphasis has been placed on optimization of the hits from virtual screening to yield potent, drug-like inhibitors. MC/FEP simulations are used to identify the most promising choices for substituents on rings, heterocycles, and linking groups. The illustrated applications center on inhibitor design for HIV-1 reverse transcriptase and SARS-CoV-2 main protease. Micromolar leads have been rapidly advanced to low nanomolar inhibitors. Key computational issues are also addressed.

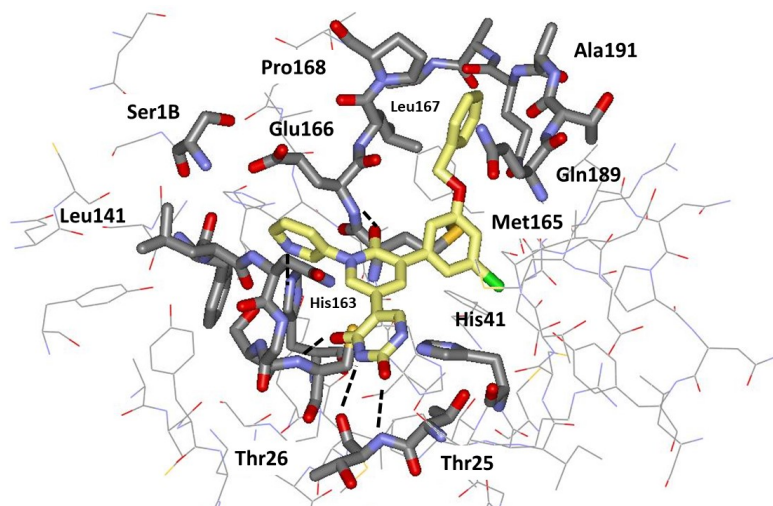


Figure 1: Rendering from a 1.8-Å crystal structure for a complex with the main protease of SARS-CoV-2. Carbon atoms of the inhibitor are in yellow.

- [1] Jorgensen, W. L. Computer-Aided Discovery of Anti-HIV Agents. *Bioorg. Med. Chem.* **2016**, *24*, 4768-4788.
- [2] Zhang, C.-H.; Stone, E. A.; Deshmukh, M.; Ippolito, J. A.; Ghahremanpour, M. M.; Tirado-Rives, J.; Spasov, K. A.; Zhang, S.; Takeo, Y.; Kudalkar, S. N.; Liang, Z.; Isaacs, F.; Lindenbach, B.; Miller, S. J.; Anderson, K. S.; Jorgensen, W. L. Potent non-covalent inhibitors of the main protease of SARS-CoV-2 from molecular sculpting of the drug parampanel guided by free-energy perturbation calculations. *ACS Central Sci.* **2021**, *7*, 467-475.
- [3] Ghahremanpour, M.; Saar, A.; Tirado-Rives, J.; Jorgensen, W. L. Computation of Absolute Binding Free Energies for Non-covalent Inhibitors with SARS-CoV-2 Main Protease. *J. Chem. Info. Model.* **2023**, *63*, 5309-5218.

Ligand-Protein Hydropathic Complementarity: Application to the Design of Antiviral Compounds

F. Javier Luque

Departament de Nutrició, Ciències de l’Alimentació i Gastronomia, Facultat de Farmàcia i Ciències de l’Alimentació, Institut de Biomedicina (IBUB) and Institut de Química Teòrica i Computacional (IQTUB), Universitat de Barcelona

Elucidating the correct binding mode of drug-like compounds is crucial to reveal the molecular determinants underlying the recognition by the target protein and to estimate the binding affinity, thus guiding ensuing hit-to-lead optimization. However, identifying the near-native binding pose in docking experiments remains a major hurdle in structure-based drug design.

Assuming that the hydropathic complementarity principle is the major driving force in ligand-protein recognition [1], the suitability of simple hydropathicity-based scoring functions to reveal the near-native pose will be discussed [2]. To this end, a benchmarking dataset of 1000 ligand-protein complexes purposely designed to encompass bioactive and decoy poses was used to assess the performance of 3D hydropathicity atomic descriptors derived from empirical and quantum mechanical models. This strategy led to a predictive accuracy of ca. 90% when the non-negligible influence of the conformational stress is also considered. The results reveal the need to leverage an understanding of nonpolar/polar chemical features for the successful discrimination of the near-native pose.

This approach can be valuable to estimate the maximum affinity that can be attained by targeting a specific binding pocket and to disclose the key determinants that must be fulfilled by active compounds, complementing the description based on the analysis of intermolecular interactions. Furthermore, it may be valuable to explore the structure-activity relationships within series of structurally-related compounds. Ongoing efforts are addressing this range of applications, which will be illustrated through the prediction of the binding mode of compounds targeting pharmacologically relevant proteins, such as soluble epoxide hydrolase [3] and hemagglutinin [4].

Acknowledgements: Support from Spanish Ministerio de Ciencia, Innovación y Universidades (PID2023-147942OB-I00 MICIU/AEI/10.13039/501100011033; María de Maeztu CEX2021-001202-M), Generalitat de Catalunya (2021SGR00671) and Consorci de Serveis Universitaris de Catalunya (project Molecular Recognition) are acknowledged.

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- [2] Medel-Lacruz, B.; Zamora, W.J.; Herrero, E.; Kellogg, G.E.; Selent, J.; Vázquez, J.; Luque, F.J. *NPJ Drug Discov.* **2026**, *3*, 18.
- [3] Vázquez, J.; Ginex, T.; Herrero, A.; Morisseau, C.; Hammock, B.D.; Luque, F.J. *J. Chem. Inf. Model.* **2023**, *63* (10), 3209–3225.
- [4] Valdivia, A.; Rocha, M.; Luque, F.J. *ACS Med. Chem. Lett.* **2025**, *16* (1), 126–135.

Exploring Quantum Algorithms for Machine Learning and Quantum Chemistry on Quantum Computers

Dennis Salahub

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T2N 1N4

For the last few years my group has been exploring the use of machine-learning (ML), in the study of nanocatalysis, with some forays into drug discovery. A main general result is that the active learning (AL) paradigm is often very efficient at discovering materials with optimal properties or optimizing nanoparticle structures. We have also explored the use of quantum ML (QML) algorithms, comparing with their classical counterparts.

On a second theme, quantum chemistry is often highlighted as one of the most promising fields for the use of quantum computers. Indeed, the field is advancing rapidly with a significant focus on (Unitary) Coupled Cluster methods providing encouraging results for some molecules. We have recently undertaken a study aimed at determining the performance of quantum algorithms for multi-determinantal (strongly correlated) quantum chemistry linking standard quantum platforms (Qiskit, PennyLane) with the OpenMolcas code.

Progress along these two fronts will be reported, with an eye to future applications to molecular interactions in biology.

Acknowledgements: Support from the Natural Sciences and Engineering Research Council of Canada (Discovery Grants), and the National Research Council of Canada (AI for Design and Applied Quantum Computing Challenge programs) is gratefully acknowledged, as is the provision of computational resources from the Digital Research Alliance of Canada.

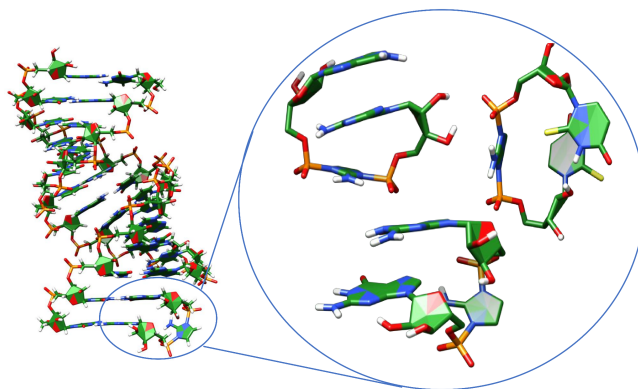
Machine Learning Potentials for Chemistry and Dynamics of RNA and DNA

Rafał Szabla, Michał Pocheć, Barbara Tomyślak, Boluwatife Ogunnaiya

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Accurate modelling of nucleic acids is one of the biggest challenges for computational chemistry, owing to their highly negatively charged sugar-phosphate backbone and the richness of intra and intermolecular interactions affecting their 3D structure and dynamics [1]. With this respect, contemporary classical force-fields are still very inaccurate in describing a broad scope of non-canonical and functional structures, whereas the application of density functional theory is limited to geometry optimizations of RNA/DNA oligomers with up to 15 residues in implicit solvent. In this talk, I will present our approach to training of highly efficient and accurate machine learning potentials (MLPs) for nucleic acids. In particular, I will show that third generation neural network potentials [2] can grasp the long-range nature of key interactions stabilizing the 3D structure and approach the accuracy of the best DFT approximations, with very favourable scaling. Most importantly our MLPs are transferable to alternative nucleic acids (XNAs), which were beyond the realm of applicability of existing RNA and DNA force fields. I will also demonstrate our most recent efforts to understand the mechanisms of nonenzymatic self-replication of RNA and its alternative forms [3, 4].

Imidazolium activated dinucleotides



Molecular Dynamic Simulations

Figure 1: Nonenzymatic RNA self-replication with imidazole-activated nucleotides.

Acknowledgements: Support from EU grant No. 12345 is acknowledged. Calculations were performed at the Wrocław Centre for Networking and Supercomputing.

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- [4] Lech, B.; Ogunnaiya, B.; Petrusevich, L.; Szabla, R. *ChemSystemsChem*, **2025**, *7*, e202400086.

Accelerated Surface Hopping MD via Scaling of Spin-Orbit Couplings: Opportunities for Machine Learning and Applications

Jakub Martinka¹, Mahesh Kumar Sit¹, Pavlo O. Dral³, Wasif Baig Mirza¹, Marek Pederzoli¹, Mojmir Kyvala³, Jiri Pittner¹

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Surface hopping (SH) methods are typically employed to simulate ultrafast nonadiabatic processes, but long timescales often remain beyond their reach. To address this, accelerated SH scheme mitigates this limitation by scaling the driving forces of such process, in particular the spin-orbit couplings (SOCs) for intersystem crossing. However, obtaining the actual time constant requires extrapolation from several ensembles of trajectories with different scaling factors. This introduces a significant computational demand, often restricting the number of trajectories per ensemble and, therefore, reducing the statistical confidence in the resulting time constant. We investigate the accelerated scheme using silaethylene as a model system, evaluating various population fitting methods and extrapolation techniques. We trained machine learning models for MR-CISD potential energy surfaces (PESs) and NACs of silaethylene, and extended our rotate-predict-rotate approach to fit SOCs. These models demonstrate high performance, yielding populations within the confidence interval of the reference MR-CISD/SA-CASSCF(2,2) data; however, the extrapolation itself is highly sensitive to the fitted time constants, limiting the accuracy of the final time constant.

A computational study of I-BODIPY (2-ethyl-4,4-difluoro-6,7-diiodo-1,3-dimethyl-4-bora-3a,4a-diaza-s-indacene) has been carried out to investigate its key photophysical properties as a potential triplet photosensitizer capable of generating singlet oxygen. Time-dependent density functional theory (TD-DFT), possibly within the Tamm–Dancoff approximation (TDA), using several exchange-correlation functionals has been tested on I-BODIPY against ADC(2), both employing a basis set with a two-component pseudopotential on the iodine atoms. Subsequently, excited-state MD simulations including both nonadiabatic effects and SOCs, employing the scaling acceleration technique, have been performed to investigate the relaxation processes in I-BODIPY after its photoexcitation to the S1 state. The TSH MD simulations revealed that intersystem crossings occur on a time scale comparable to internal conversions and that after an initial phase of triplet population growth a “saturation” is reached where the ratio of the net triplet to singlet populations is about 4:1. The calculated triplet quantum yield of 0.85 is in qualitative agreement with the previously reported experimental singlet oxygen generation yield of 0.99 ± 0.06 .

Multivalent Metal Ions, Proteins and Drugs

Ran Friedman

Linnaeus University, Kalmar, Sweden

Many metal ions are indispensable in human biology. Some ions are even used for therapeutic purposes. Others, naturally present in the body, might interact with drugs. In my talk, I will discuss examples of both. Firstly, I will present some radioactive ions that are used as cancer therapy, where computational work was carried out to examine their off-target binding and risk for toxicity. [1] In the second part of my talk, I will discuss interactions between ions and antibiotics, [2] and whether the interactions with biotic ions contribute to the toxicity of fluoroquinolone antibiotics. All of the presented results are based on quantum-chemical calculations using DFT.

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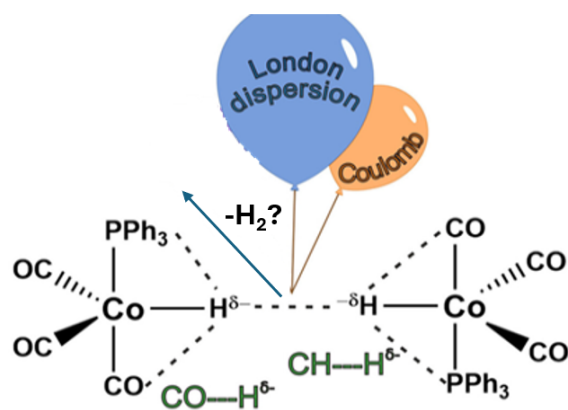
[2] Friedman, R. *Phys. Chem. Chem. Phys.* **2026**, *28* (12), 7534–7540.

Theoretical Description of Hydride-Hydride Interactions in Selected Hydrogen Storage Materials

Mariusz P. Mitoraj, F. Sagan, R. Filas, A. Ptaszek, P. Kubisiak

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In recent years there has been growing interest in the use of metal hydrides as hydrogen rich sources. [1,2] The high content of hydride-hydride contacts $H^{\delta-} \cdots^{\delta-} H$ in these materials appears to be relevant for dihydrogen formation.[1,2] Structural studies allowed to formulate so-called "2 Å rule" stating that the minimum HH distance in metal hydrides is often 2 Å, which is indicative of the repulsive nature of such interactions [1,2]; it is also in accord with the chemical intuition since negatively charged ions repel each other. [1,2]



Accordingly, the present talk will address this issue by shedding light on physical factors which constitute homopolar hydride-hydride interactions $H^{\delta-} \cdots^{\delta-} H$ in the experimentally known transition metal hydride complexes i.e. $HCoL_4$, $L = CO, PPh_3, PH_3$. [3,4,5] In order to achieve this goal, the charge and energy decomposition ETS-NOCV approach along with Interacting Quantum Atoms (IQA) analysis have been applied for the adducts $L_4CoH \cdots HCoL_4$. [3,4] The results will be discussed in the light of more standard hydrogen bonds and polar dihydrogen interactions of the type $AH^{\delta+} \cdots^{\delta-} HB$. Mechanism of dehydrogenation of $HCo(CO)_4$ will be also discussed based on static and molecular dynamics simulations. [3,4]

Acknowledgements: M.P.M. acknowledges the financial support from the NCN grant (ST4/00104).

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- [5] a) Mitoraj, M. P. et al. *J. Chem. Theory Comput.* **2009**, *5*, 962–975; b) ADF 2022.1, SCM, Theoretical Chemistry, Vrije Universiteit, Amsterdam, The Netherlands, <http://www.scm.com> *J. Chem. Phys.* **2025**, *162*, 162501, 1–47; c) Kozyra, P. et al. *J. Phys. Chem. C* **2013**, *117*, 7511–7518.

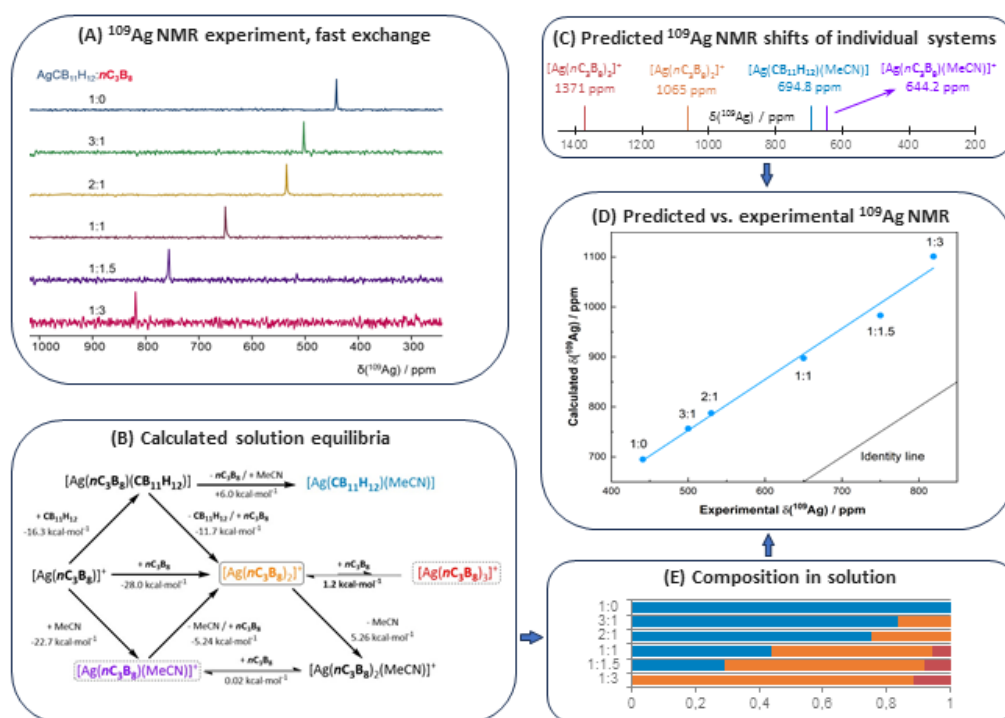
Solvation, Aggregation, and the Predictive Power of ^{109}Ag NMR Calculations in Silver–Carborane Systems

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Heavy-element NMR shifts are exceptionally sensitive to relativistic effects and the local coordination environment, making them both challenging computational targets and potentially powerful structural probes. Here, we combine ^{109}Ag NMR experiments with relativistic SO-ZORA calculations to characterize solution equilibria in edge-bound silver–carborane assemblies. Reactions of nido-7,8,9- $\text{C}_3\text{B}_8\text{H}_{10}$ derivatives with Ag(I) salts in MeCN generate dynamic mixtures of $[\text{Ag}(\text{nC}_3\text{B}_8)]^+$, $[\text{Ag}(\text{nC}_3\text{B}_8)_2]^+$, and $[\text{Ag}(\text{nC}_3\text{B}_8)_3]^+$, supported by HRMS and ^{11}B NMR. The calculated ^{109}Ag shifts respond dramatically to explicit coordination: with implicit solvation, $[\text{Ag}(\text{nC}_3\text{B}_8)]^+$ appears at $\sim 200\text{--}300$ ppm, whereas explicit MeCN coordination shifts it to $\sim 640\text{--}850$ ppm. Additional carborane coordination produces further deshielding, to $\sim 1000\text{--}1060$ ppm for $[\text{Ag}(\text{nC}_3\text{B}_8)_2]^+$ and $\sim 1290\text{--}1500$ ppm for $[\text{Ag}(\text{nC}_3\text{B}_8)_3]^+$. Population-weighted shifts based on calculated solution free energies reproduce the experimental downfield trend, showing that the observed resonance reflects rapid exchange among solvent- and carborane-bound Ag(I) species rather than a single static complex. Thus, quantitative interpretation of ^{109}Ag NMR requires explicit ligand treatment and ensemble averaging, while its wide shift range makes ^{109}Ag NMR a sensitive probe of Ag(I) coordination.



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Revisiting “Intuitive” and “Counter-intuitive” Interactions: New Insights

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The use of the electrostatic potential $V(\mathbf{r})$ in chemistry was pioneered by Scrocco and Tomasi in the 1970’s as a tool for understanding the ensuing interactions that might occur between molecules. Such interactions were generally between a negative region on one molecule and a positive region on another, what we consider as “intuitive” interactions. [1,2] In this presentation we will revisit both what can be called “intuitive” and “counter-intuitive” interactions. [1,2,3,4] Our computational procedure involves changing iso-density envelopes upon which to plot the electrostatic potential to address both the strengths of intermolecular and intramolecular interactions. [3,4]

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Oxidation-State-to-Coordination-Number Ratio Predictor of Hydrogen Bonding Strength in the Second Coordination Sphere of Metal Complexes

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Coordination of ligands influences properties of ligand, including their hydrogen bonds in the second coordination sphere. These hydrogen bonds of metal complexes play a crucial role in a wide range of fields, including catalysis, biochemistry, molecular recognition, materials science, metal separation, medicinal chemistry, synthesis, and environmental science.

This work investigates hydrogen bonds of coordinated ligands. The study combines analysis of crystal structures from the Cambridge Structural Database with high-level quantum-chemical calculations. The results demonstrate that coordination to a metal ion profoundly alters the hydrogen-bonding properties of ligands by redistributing their electron density. As a consequence, coordinated ligands become stronger hydrogen-bond donors and weaker hydrogen-bond acceptors than their non-coordinated counterparts.

The quantum chemical calculations of hydrogen bonds were performed on large number of metal complexes enabling to observe influence of several factors. [1,2] The calculated trends are in excellent agreement with those observed in crystal structures. Among factors, the charge of the complex has the greatest influence, with charged complexes forming substantially stronger hydrogen bonds. Ligand type also has a significant effect, whereas the atomic number of the metal has only a minor influence. Very interestingly, the results reveal that hydrogen-bond strength is governed by the combined effect of the metal oxidation state and coordination number, which is expressed by the oxidation state-to-coordination number (OS/CN) ratio. An increase in the OS/CN ratio enhances the donor ability of coordinated ligands while reducing their hydrogen-bond acceptor strength. The data show that OS/CN ratio can be used to predict strength of hydrogen bonds.

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Use of Static and Dynamic Catalytic Fields to Validate Alternative Enzyme Reaction Mechanisms and Explain the Catalytic Role of Zero-Point Vibrations

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Modeling enzyme-catalyzed reactions requires assumptions that may lead to alternative reaction mechanisms characterized by different static catalytic fields. These fields can be compared with the pattern of conserved charged residues in the enzyme active site, providing a means of validating alternative reaction mechanisms. [1]

Among all enzymes, many exhibit exceptionally high catalytic activity, characterized by extremely large turnover numbers. According to the hypothesis proposed by Houk et al., this extraordinary catalytic efficiency may be related to the formation of covalent bonds between the enzyme active site and the transition state. [2] However, the detailed mechanism underlying such exceptional catalytic activity has not yet been fully explained. A characteristic feature of active sites of these enzymes is the presence of hydrogen bond networks, including very short and therefore strong ones, which may possess significant covalent character. [3] Such short hydrogen bonds exhibit a single-well asymmetric potential, in which proton displacements are driven solely by the proton's zero-point vibrations.

Here, the catalytic role of these zero-point proton oscillations is analyzed for ketosteroid isomerase using dynamic catalytic fields. [4] The results clearly demonstrate the importance of synchronous proton displacements in opposite directions, which are required to catalyze the consecutive steps of the reaction.

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Mechanisms of F₄₃₀-Catalyzed Dehalogenations Revealed by Theoretical Calculations

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Degradation of organic pollutants by metal coenzyme purified from organisms is a frontier research field in both environmental science and bioinorganic chemistry. Methanogens, which are widely distributed in nature, have been proved to be powerful in reductive dehalogenation, while F₄₃₀ coenzyme has been proved to play a key role. However, the mechanism of reductive dehalogenation reaction by F₄₃₀ coenzyme has not been revealed yet. We have, therefore, performed calculations to reveal the complex F₄₃₀ dehalogenation mechanism using quantum chemical methods. Model systems include halogenated alkanes, and alkenes. For this purpose we have carried out benchmark studies [1] on the dehalogenation of chloromethane by octaethylisobacteriochlorin, a model of F₄₃₀ coenzyme, for which experimental data is available. Based on these studies MN15-L/def2-TZVP theory level has been selected for further studies.

We have characterized alternative mechanisms of F₄₃₀-catalyzed dehalogenation of chloromethanes and chloroethenes and associated isotope effects of chlorine, carbon and hydrogen. These results indicate a shift in the mechanism with the increasing number of chlorine atoms in chloromethanes. Details of the obtained results will be discussed.

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Exploring the Myostatin Activation Pathway: A Promising Target for Treating Muscle Atrophy

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Skeletal muscle is the predominant muscle tissue in the human body, covering the skeleton and connecting to bones through tendons that enable muscle contraction and movement. Among the key proteins involved in muscle development and homeostasis, the growth and differentiation factors GDF-11 and GDF-8 play central roles. GDF-8 (myostatin) acts as a negative regulator of skeletal muscle growth by suppressing signaling pathways responsible for muscle fiber formation and regeneration. Consequently, myostatin inhibition has emerged as a promising therapeutic strategy for the treatment of muscle-wasting disorders, including amyotrophic lateral sclerosis and spinal muscular atrophy. In addition, reversible myostatin inhibitors could help mitigate muscle atrophy in astronauts during prolonged exposure to microgravity, thereby supporting long-duration space missions. Although the activation and inhibition mechanisms of myostatin have been extensively investigated and the structures of its major protein complexes have been elucidated, no reversible myostatin inhibitors have yet been approved for human therapy. In this context, the present study focuses on the rational design of myostatin inhibitors, including both small molecules and peptides, through a detailed understanding of the intermolecular interactions governing the different myostatin-associated complexes involved in the signaling pathway.

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Noncovalent Weak Interactions with DFT: From Molecules to Biogenetic Crystals

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Weak non-covalent interactions are ubiquitous in chemistry, yet they remain a challenging problem for most density functional approximations. The inclusion of empirical dispersion corrections has proven to be an effective strategy for overcoming many of these limitations. However, these approaches may exhibit shortcomings when applied to nonstandard systems, such as molecules far from equilibrium or large molecular clusters. In this presentation, we will discuss these issues through a series of examples, ranging from isolated molecular systems to biologically relevant molecular crystals [1,2]. We will also present alternative approaches, developed within the framework of density functional theory, that provide a more physically grounded description of these challenging interactions [3,4].

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How Does Microhydration Affect the Dissociative Electron Attachment? MD, QM and Experimental CEMB Studies on 8-(trifluoromethyl)thioadenine in Water Clusters

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Radiotherapy is one of the most widely used anticancer treatments; however, its effectiveness is often limited in radioresistant, hypoxic tumors. To enhance radiotherapy, radiosensitizers can be employed. Among the most thoroughly studied groups of radiosensitizers are modified uracils, but the other nucleobases derivatives, able to exploit low-energy electrons generated by ionizing irradiation, have also been investigated. 8-(trifluoromethyl)thioadenine (ASCF₃) is an example of a purine-based compound with potential radiosensitizing properties. To function as an effective radiosensitizer, such compounds should generate a reactive nucleobase radical via the dissociative electron attachment (DEA) process.

With the use of molecular dynamics simulations, quantum chemical calculations and crossed electron-molecular beam (CEMB) experiments, we analyzed the DEA mechanism of ASCF₃ in the gas phase [1], a microsolvated environment (clusters containing one to four explicit water molecules), and bulk water. Our results demonstrate that, upon electron attachment, ASCF₃ anion radical undergoes spontaneous or low-barrier releasing of a CF₃[−] anion, yielding the desirable AS• radical, both in the gas phase and under microsolvated conditions. We observe that lower temperatures (100-200 K) support the stability of ASCF₃ clusters with water; on the other hand, we suggest that ASCF₃ immersed in water tends to undergo untypical DEA process, resulting in HF detachment and formation of a cyclic ASCF₂(-H) product.

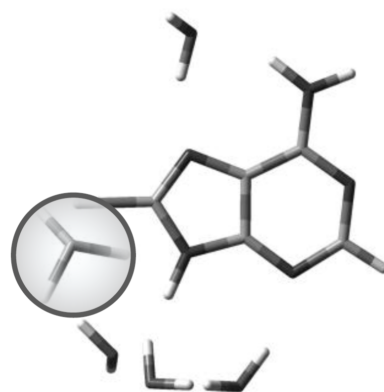


Figure 1: Optimized geometry of anion radical ASCF₃ in four water molecules cluster. CF₃[−] anion detached circled.

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Approximate Electronic-Structure Methods for Charge Transport in Biomolecular Junctions

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The charge-transport properties of biomolecular systems are governed by molecular structure, chemical composition, the presence of redox-active sites, their local environment, and thermal fluctuations, all of which are affected by coupling to the surrounding environment. These factors are closely connected to the electronic response of the systems to external fields and potentials. In biomolecular junctions between metal contacts, the alignment between molecular electronic states and the Fermi level of the metal is an additional key factor, so both the mechanism and efficiency of transport can change markedly with the environment. For example, redox proteins commonly transfer electrons by a hopping mechanism in biological environments, but they support long-range quantum tunneling in metallic junctions [1,2].

Non-equilibrium Green's function methods (NEGF) combined with electronic-structure approaches such as density functional theory (DFT) are widely used to calculate tunneling currents and conductance. However, their computational cost limits direct application to biomolecular junctions, where structural complexity and dynamical effects are essential. Approximate but reliable methods are therefore needed, including semi-empirical and tight-binding Hamiltonians, band-alignment corrections, approximate electrode self-energies, and linear-response treatments of external fields [3]. In this contribution, I will discuss the accuracy and applicability of these approximate techniques for biomolecular junctions (Fig. 1), with emphasis on key factors controlling the charge-transport behavior.

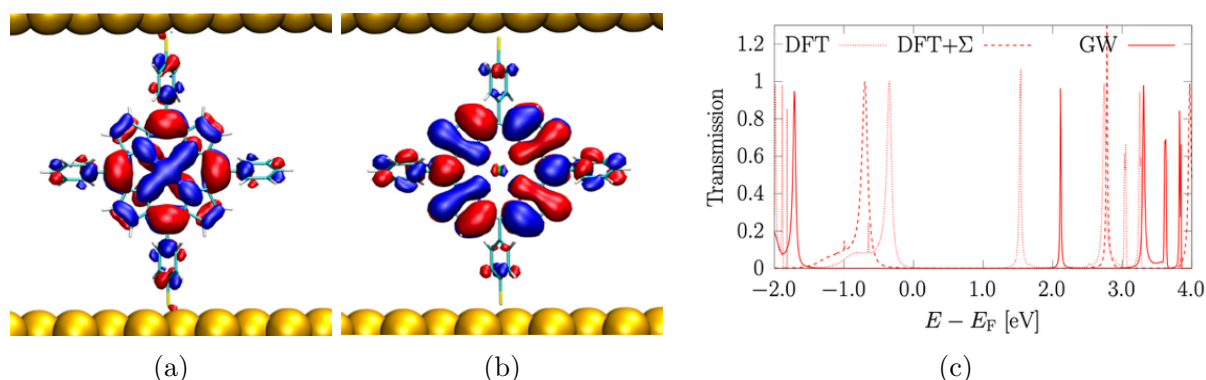


Figure 1: Frontier orbitals of the Fe(II)-5,10,15,20-tetraphenyl porphine (FeTPP) gold junction: HOMO (a), LUMO (b), responsible for the transport, and the related transmission function (c)

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Charge Transport on Heterogenous Bio/Metallic Interfaces

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Redox proteins are promising building blocks for bioelectronic devices due to their ability to support long-range electron transport. However, the mechanisms governing charge transport across protein-electrode interfaces remain poorly understood. In this work, multiscale simulations combining molecular dynamics, density functional theory, and transport calculations are used to investigate electron transport in protein junctions [1].

Cytochrome b562 (Cyt-b562) is employed as a model single-heme protein to examine the role of the protein environment, electrode coupling, and external perturbations on conductance. The results show that transport is primarily controlled by protein-electrode interactions and off-resonant protein states rather than direct transport through heme cofactor [2,3]. To evaluate computational approaches for transport calculations, the Projector Operator Diabatization (POD) method is benchmarked against Non-Equilibrium Green's Functions (NEGF) calculations for Cytochrome c (Cyt-c) molecular junctions, demonstrating good agreement in transport pathways and conductance trends [4]. Finally, electron transport in multi-heme protein Small Tetraheme Cytochrome (STC) is investigated using Marcus hopping theory, revealing efficient charge migration through coupled heme networks.

Together, these results provide a unified picture of biological electron transport, highlighting and transition from coherent tunnelling in single-heme proteins to thermally activated hopping in multi-heme systems.

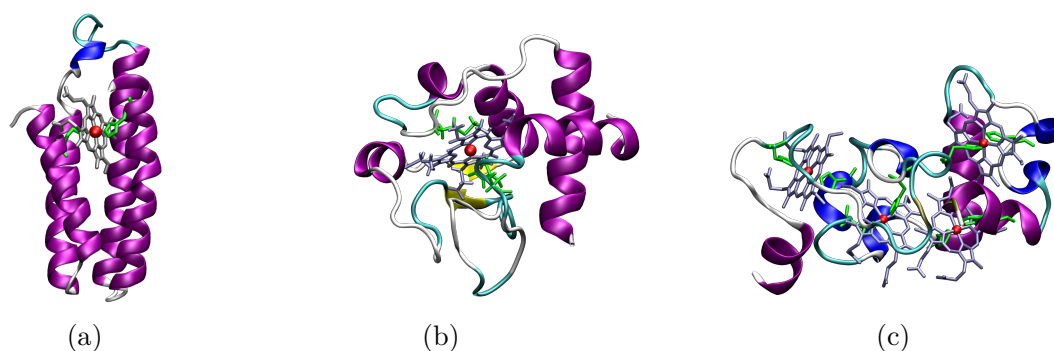


Figure 1: Crystal structures of the three protein systems studied in this work: (a) Cytochrome b562 (PDB: 2BC5), (b) Cytochrome c (PDB: 1G1W), (c) Small tetraheme cytochrome (PDB: 1M1Q). Heme cofactors show in iceblue with Fe cations (red spheres) and axial ligands (green)

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Computational Studies of Enzyme Catalysis: Toward the Design of Novel Therapeutics

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Computational chemistry techniques that combine quantum chemistry and classical molecular mechanics (QM/MM) have been extensively applied to the study of enzyme catalysis. The integration of these approaches with experimental methods has enabled a detailed understanding of the reaction mechanisms of these complex yet highly efficient biocatalysts at the molecular level. This synergy has opened new avenues for the rational design of enzyme inhibitors with potential therapeutic applications, as well as for the engineering of novel enzymes for industrial purposes, such as the depolymerization of plastics.

In this contribution, we will present recent results from computational studies performed in our laboratory in close collaboration with experimental groups, highlighting the use of molecular simulations for the rational design of enzyme inhibitors. Our research has focused on cysteine proteases implicated in a range of diseases and infectious processes. By combining detailed mechanistic characterization of the inhibition process with analyses of the electrostatic and steric determinants of enzyme-inhibitor interactions, we have developed strategies for the rational optimization of inhibitor potency and selectivity. [1-6]

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Light in Medical Treatments: Mechanistic Insights from Computations

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Medical techniques based on the use of light for activating the drug are occupying a prominent place in cancer treatment due to their selectivity that contributes to reducing undesirable side effects of conventional chemotherapy. Among these therapeutic treatments, photodynamic therapy (PDT) and photoactivated chemotherapy (PACT) are emerging as complementary approaches for selective destruction of neoplastic tissue through direct cellular damage. Both techniques rely on the employment of a molecule, photosensitizer PS, able to absorb within the so-called therapeutic window. Thus, the exposure to light of otherwise inert molecules promotes the population of excited states of the drug, that in PDT can produce the cytotoxic species, such as $^1\text{O}_2$ and other ROS, in PACT are deputed to the active species release or formation. Many photosensitizers were proposed and explored as anticancer agents for applications in different medical approaches to improve their chemical, biological and photophysical properties [1].

In this field, also cofactors like riboflavin, essential for numerous reactions catalyzed by flavoproteins, including activation reactions of other vitamins, could play a crucial role, as it could be able to promote the photoactivation of well-designed molecules to be inert until they reach the target [2]. Depending on the chemical structure, beside the photogeneration of cytotoxic species, the action as anticancer drugs of the photosensitizers can include reversible DNA interactions by intercalation. The establishment of non-covalent π - π stacking interactions between the drug and two base pairs in the DNA major and minor groove can alter the cellular functions ultimately lead to cell death. DNA intercalative interactions of aromatic moieties are usually associated with both bathochromism and hypochromism of the absorption bands thanks to the charge transfer from DNA to the drug [3], leading to a possible shift of the drug absorption band within the therapeutic window, thus enhancing PDT efficacy. Computational investigations reveal how electronic structure, intersystem crossing kinetics, and ligand design modulate the activation pathways and biological reactivity of these systems and can contribute to the rational design of next-generation photoactive compounds with improved absorption in the therapeutic window, enhanced photostability, and optimized targeting capabilities.

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Enthalpy/Entropy Decomposition in PMF Simulations

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A detailed understanding of the self-assembly of supramolecular complexes and specific biomolecular interactions is essential for the rational design of new materials and drugs, as well as for understanding the molecular foundations of life. However, relating calculated free energies to molecular structure remains challenging.

Here, we present an extension of constrained molecular dynamics simulations that provides internal-energy and entropic contributions alongside the free-energy profile. We compare the performance of two approaches based on ensemble averages evaluated in phase space and configuration space. We also describe how the calculation of second derivatives of collective variables, required by the configuration-space approach, can be effectively avoided. The performance of the methods is demonstrated using a calix[4]arene molecular tinkertoy and selected biomolecular systems. The method is available in the PMFLib toolkit (<https://pmflib.ncbr.muni.cz>).

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Biomolecular Recognition via the MED Model: From First-Principles Scoring to Broader Biophysical Applications

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Accurately predicting binding affinities remains a persistent challenge due to the limited transferability of empirical scoring functions and the prohibitive computational cost of standard quantum chemical methods. To bridge this gap, the MED model is proposed as a physically motivated approach free of empirically fitted parameters [1]. By capturing essential long-range interaction components, specifically multipole electrostatics and nonempirical dispersion [2], the MED framework provides general and computationally efficient approximation of binding energy.

In this talk, the overall predictive capabilities and robustness of the MED model are demonstrated across a diverse array of protein-ligand systems, establishing its performance relative to classical empirical scoring methods. Building upon its documented successes in challenging targets like protein-protein interaction inhibitors [3] and scoring the catalytic activity of mutant variants [4], the broader scope of the model is discussed through its latest application examples.

In particular, preliminary insights are presented into how MED-guided interaction energy analysis can be extended to rationalize the structural basis of drug resistance mutations. Furthermore, its emerging potential beyond protein targets is explored by investigating nucleic acid microenvironments, showcasing early data on how local nucleotide sequences impact the energetics of mutagenic cytosine deamination. Together, these benchmarks and preliminary applications highlight the MED model as a versatile, physically rigorous tool for exploring complex biophysical phenomena and validating machine learning-generated biomolecular structures.

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QM-Derived Empirical Force Fields Improve DNA and Protein–DNA Simulations

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The latest addition of the OL family of force fields, OL24, improves the description of the A/B-DNA equilibrium. Existing AMBER force field variants underpopulate the north (C3'-endo) sugar pucker, compromising simulations of protein–DNA systems requiring B-to-A transitions. The OL24 refinement of deoxyribose puckering brings the A/B equilibrium into better agreement with experimental data. The description of canonical B-DNA, DNA–RNA hybrids, and protein-induced conformational adaptation is also improved. Combined with the previous α/γ correction of OL21, OL24 provides a coherent framework for general DNA and protein–DNA simulations. We also assess the compatibility of OL force fields with Electronic Continuum Correction (ECC) charge scaling and the usefulness of Lorentz-Berthelot combining rules.

Molecular Dynamics Studies of the Interactions Between Bacterial Cell Envelopes and Products of Plastic Degradation

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Microbial upcycling has recently emerged as a promising strategy to mitigate plastic pollution by converting plastic-derived compounds into value-added products such as biopolymers, fuels, and specialty chemicals. In Gram-negative bacteria, the overall efficiency of such processes critically depends on the transport of plastic degradation products across the complex cell envelope, comprising the outer membrane, peptidoglycan cell wall, and inner plasma membrane. Depending on their size and hydrophobicity, these compounds may cross the envelope either by passive diffusion or via specific membrane transport systems.

In this study, we employed classical all-atom molecular dynamics simulations to investigate interactions between bacterial membranes and representative products of plastic degradation. Due to the structural complexity of Gram-negative membranes and the lack of detailed experimental lipid composition for the studied *Pseudomonas putida* strain, we first constructed model bilayers mimicking the two bacterial membranes with systematically increasing compositional complexity. We analyzed how bilayer structure depends on lipid composition, water model, and the composition of the aqueous phase, and, for the outer membrane, we further examined the influence of lipopolysaccharide (LPS) structure on key bilayer properties.

Next, model degradation products of common plastic polymers, including monomers, oligomers, and their oxidized forms, were introduced into the membrane systems. Derivatives of petroleum-based polymers (e.g. polyethylene, polystyrene) and bioplastics (e.g. polyhydroxybutyrate, polylactic acid) were considered. We characterized membrane association and penetration of these compounds, their impact on membrane structure, and estimated permeability coefficients. These results provide molecular-level insight into the passive diffusion of plastic degradation products across Gram-negative cell envelopes and may help guide the rational design of microbial upcycling strategies.

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Evolution of Charge Sensitivities During MD Simulations

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Large molecular systems are commonly simulated at atomic resolution using molecular dynamics (MD) methods. However, the transition to an atomistic description is generally accompanied by the loss of valuable information related to electronic degrees of freedom. Nevertheless, such information can be recovered from MD trajectories. One suitable approach for this purpose is the Electronegativity Equalization (EE) formalism [1]. In some applications, the EE equations are incorporated directly into MD simulations. While their numerical solution yields atom-centered charges, it simultaneously discards important information concerning the electronic reactivity of the system.

Depending on the computational variant employed, the EE formalism provides access to a broad range of electronic descriptors, including electronegativities, hardness and softness parameters, Fukui functions, linear response matrices, and related reactivity indices. Furthermore, the EE framework offers considerable flexibility in defining equilibrium conditions, making it possible to distinguish between direct (diagonal) and indirect (off-diagonal) effects.

In this presentation, we illustrate various molecular susceptibilities for selected molecular systems. Three types of equilibrium conditions are considered: (i) global equilibrium, (ii) equilibrium in polarized molecules, and (iii) equilibrium of selected reagents embedded within a molecular environment.

Acknowledgements: Calculations were performed at CYFRONET AGH Supercomputer Centre: Grant No PLG/2025/018364.

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Asset of Separability for QC-Inspired Polarizable Intermolecular Potentials

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Separability is a major asset for QC-inspired polarizable potentials. We benefit from SAPT-DFT, a perturbation procedure which constructs E_{int} as a sum of six distinct contributions, including explicit charge-transfer and exchange-dispersion [1, and Refs. therein]. The SIBFA potential [2,3] embodies all six contributions. For a series of molecular fragments constitutive of proteins and nucleic acids, the relevant atom-type specific parameters for each contribution were reoptimized in order to reproduce by LSQF its SAPT-DFT counterpart upon performing in- and out-of-plane radial and angular variations of the approach of water and of a Zn(II) probe for each target atom. We present the outcome for dimethyl phosphate (DMP-), the constitutive of the phosphodiester backbone of DNA and RNA. Validations are performed on its complexes with Zn(II) and eight water molecules. Starting with gauche-gauche (gg) 'native' conformation, a diversity (16) of starting structures are considered and energy-minimized. Energy-minimization is performed similarly on the gauche-trans (gt) and trans-trans (tt) conformations, on a conformation intermediate between gg and gt, and another between gt and tt. A total of 80 complexes is thus derived, which differ very significantly in the DMP-cation binding mode, whether direct to an anionic or to a ester O, or water-mediated. Single-point MP2 and DFT-d calculations are performed and reported enabling to validate the SIBFA predictions. Related validations are also recalled concerning the complexes of ligands to extended recognition sites of Zn-metallo-enzymes, emphasizing the need for a proper control of non-additivity. Finally, a brief update is given concerning our project of selective base-pair sequence targeting in the major groove of DNA [4,5], as it now involves collaborations with experimentalists in five Laboratories.

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Probing Pseudopotential Artifacts Through the Lens of Non-Covalent Interactions

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Plane-wave density functional theory calculations frequently rely on the projector-augmented wave (PAW) method [1] or pseudopotentials to bypass tightly bound core electrons efficiently. However, standard validation metrics primarily focus on the properties of elemental solids. These traditional benchmarks consistently overlook subtle precision losses in modeling delicate non-covalent interactions (NCIs), leaving a critical gap in the validation of potentials used for molecular crystals, supramolecular chemistry, and biomolecular simulations. This work utilizes the S66 [2] and X40 [3] benchmark datasets to systematically diagnose PAW and pseudopotential errors across diverse interaction regimes. By evaluating interaction energy deviations relative to Gaussian-type orbital (GTO) basis sets at the complete basis set limit—incorporating exact two-component (X2C) scalar relativistic effects at the PBE level—we reveal that these errors are highly systematic. While dispersion-dominated complexes suffer relatively minor deviations, hydrogen-bonded and halogen-bonded systems exhibit significant interaction energy errors. The primary cause of these errors is an inaccurate description of the electron density within the investigated systems. For highly electronegative atoms (F, O, N), this density error can be approximated by a set of local dipoles. Applying a simple electrostatic correction to the intermolecular interaction energies successfully quenches the Soft potential error by nearly 80% for the water dimer (reducing the error from -9.6 to -2.1 meV). For hydrogen-bonded systems where PAW errors are largest, this proposed correction reduces the errors of the Soft potential to the level of the Standard potential [4]. Crucially, this simple dipole-based correction breaks down for heavier halogens. In halogen bonding, the density error loses its pristine p -like symmetry, manifesting instead as a severe, anisotropic over-depletion of the σ -hole along the covalent bond axis. Finally, by means of multipole models, we show that the apparent high precision of uncorrected potentials for halogen-bonded systems is actually an artifact of error cancellation between electrostatic and residual overlap errors.

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Uncovering Solar Panel Defects with an EPR Probe

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One of the major challenges for fullerene containing solar cells is the degradation of the fullerene layer over time [1,2]. In this work a new analytical method is suggested for the study of the degradation products of C₆₀ and its derivatives in solar panels. N@C₆₀ doped into the C₆₀ layer could mimic the C₆₀ properties during degradation, while simultaneously providing a distinct nitrogen radical EPR signal. We show in our DFT calculations that certain oxidation defects cause the central nitrogen position to become energetically unfavorable, drastically changing the EPR spectra due to nitrogen-cage bonding. This new method, when used alongside other spectroscopy methods, could help identify formed degradation products, uncovering the chemistry behind the degradation process.

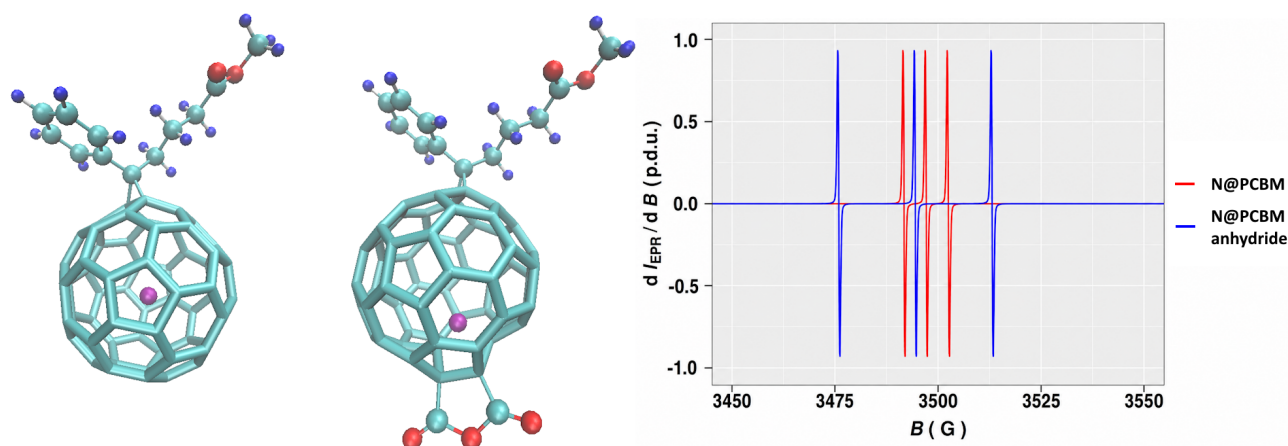


Figure 1: Simulated EPR spectra of optimized ⁴N@PCBM (left) and ²N@PC₅₈BM anhydride (middle)

Acknowledgements: This work has received support from the Czech Science Foundation (Grant No. 26-20375S)

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Estimation of Charge-Transfer Excitation Energies from Energy Decomposition Analysis

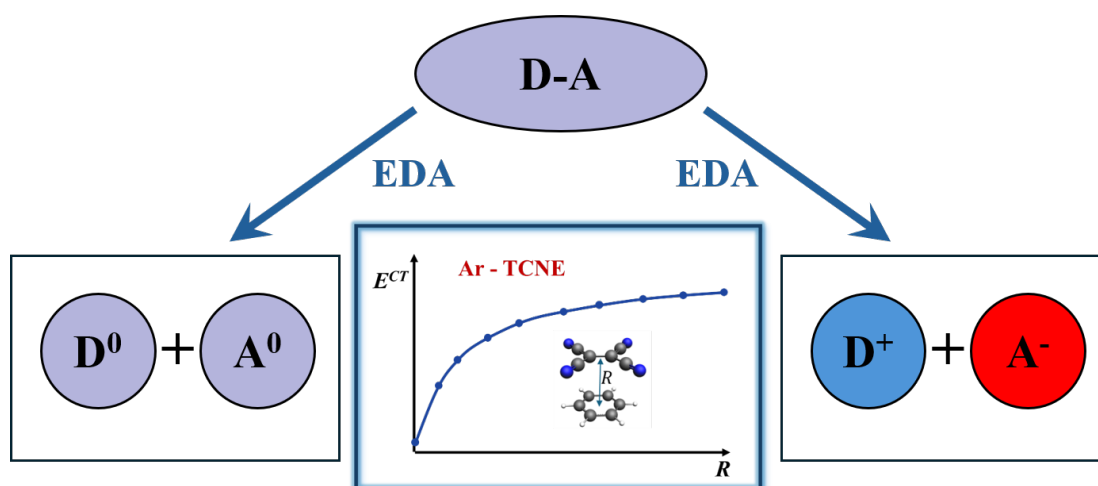
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We present a computationally efficient method for estimating inter-molecular charge-transfer (CT) excitation energies based on energy decomposition analysis (Extended-Transition-State, ETS). This approach evaluates CT energies from based on ground-state density functional theory calculations only, with neutral and charge-separated fragmentations at fixed geometry, i.e. without explicit excited-state calculations. The CT energy is obtained by combining fragment ionization potential and electron affinity terms with electrostatic and Pauli repulsion contributions obtained from ETS analysis. The proposed approach correctly reproduces the asymptotic behavior of CT excitation energies. Benchmark results for a variety of CT complexes show relatively good agreement with experimental reference values across several exchange–correlation functionals, including generalized gradient approximations. The ground-state orbital-interaction term can form a basis for a simple correction that can significantly improve accuracy. The method provides a low-cost framework for analyzing CT energetics in weakly interacting donor–acceptor systems.

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Combining Deformation of Molecular Electrostatic Potential with NOCV Orbitals: The Δ MEP-NOCV Approach

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Here, we introduce the Δ MEP-NOCV method, which combines the deformation of the molecular electrostatic potential (Δ MEP) [1,2] with the Natural Orbitals for Chemical Valence (NOCV) [3] framework. This approach complements conventional density-based bonding analyses by providing a direct electrostatic picture of electron redistribution upon bond formation.

Δ MEP is defined as the difference between the MEP of AB and its promolecule, where fragments A and B retain their isolated electronic structures at the final geometry (1). Since nuclear contributions cancel in this representation, Δ MEP directly reflects the electrostatic effect of electron-density deformation upon bond formation.

$$\Delta V(\mathbf{r}) = V^{AB}(\mathbf{r}) - V^A(\mathbf{r}) - V^B(\mathbf{r}) = - \int \frac{\Delta\rho(\mathbf{r}')}{|\mathbf{r}' - \mathbf{r}|} d^3r' \quad (1)$$

By employing the NOCV decomposition of the deformation density, $\Delta\rho$, the total Δ MEP can be partitioned into contributions associated with individual NOCV orbital pairs (2).

$$\Delta V(\mathbf{r}) = - \int \frac{\Delta\rho(\mathbf{r}')}{|\mathbf{r}' - \mathbf{r}|} d^3r' = - \int \frac{\sum_k^{n/2} \Delta\rho_k(\mathbf{r}')}{|\mathbf{r}' - \mathbf{r}|} d^3r' = - \sum_k^{n/2} \int \frac{\Delta\rho_k(\mathbf{r}')}{|\mathbf{r}' - \mathbf{r}|} d^3r' \equiv \sum_k \Delta V_k(\mathbf{r}) \quad (2)$$

Each Δ MEP component thus represents a chemically interpretable bonding channel, such as σ/π interactions or donation/back-donation effects. This enables a direct connection between density redistribution, electrostatic potential changes, and orbital interaction energies obtained within the ETS-NOCV [2,4] energy decomposition scheme (Fig. 1).

Overall, the proposed Δ MEP-NOCV methodology provides a compact electrostatic complement to ETS-NOCV analysis, enabling a clearer interpretation of how specific orbital interactions contribute to bond formation.

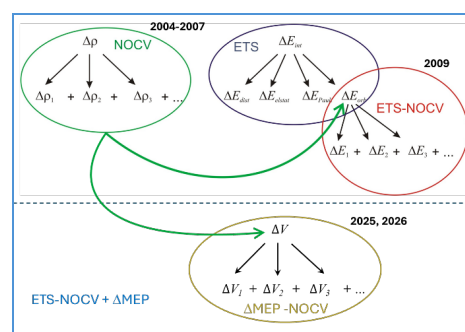


Figure 1: The idea of the integrated ETS-NOCV + Δ MEP approach.

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Accelerating Quantum Embedding for Accurate QM/MM Calculations

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Quantum mechanics/molecular mechanics (QM/MM) is the standard method for modelling chemistry in large molecular systems, particularly in enzyme catalysis. However, achieving converged energetics often requires a large QM region, which limits the scale of QM/MM simulations because of computational cost. In addition, calculating kinetic and thermodynamic properties requires extensive sampling, which in turn demands QM methods that can evaluate energies and forces efficiently.

To address this bottleneck, we introduce the local embedded subsystem (LESS) approach. LESS extends our wavefunction embedding scheme and enables hybrid [1] and double-hybrid [2] DFT accuracy at the cost of only a few core hours, even for large QM regions, tested up to nearly 400 atoms. Its key feature is the optimisation of auxiliary basis functions for the embedded active subsystem, combined with cost-effective DFT treatment of a larger environment.

The applicability of LESS has been demonstrated for the challenging phosphate-catalytic enzyme Ras [3], as well as for homogeneous and heterogeneous catalysis, resulting in speed-ups of up to two orders of magnitude with embedding errors of only a few tenths of a kcal/mol. Our new gradient implementation for LESS enables reaction path optimisations with methods approaching chemical accuracy. To further improve and guide models of enzyme reactivity, we also developed the Locality Accelerated and Systematically Improvable (LASI) scheme [4], which is designed to provide affordable free energy calculations. Together, these tools improve the reliability of QM/MM calculations and bring them closer to experimental kinetic and thermodynamic measurements.

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Thermodynamic principles behind H-atom abstraction mechanisms and reactivities

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The influence of thermodynamics on chemical reactivity is remarkably rich and multifaceted. Here, we introduce the concept of off-diagonal thermodynamics and explore its role in concerted H-atom abstraction reactions through two distinct case studies.

First, we demonstrate that hydride-coupled electron transfer (HCET) represents a fundamentally distinct mechanistic alternative to proton-coupled electron transfer (PCET). By establishing a direct connection between the PCET and HCET thermodynamic cycles and H-atom abstraction reactivity, we show that the dominant mechanism is governed by the cycle with the more favorable off-diagonal thermodynamics. These findings are further corroborated by intrinsic bond orbital analyses.[1]

Second, we show that the redox versus acid–base potential disparity of tyrosine, which provides a key thermodynamic basis for reaction asynchronicity, can be quantified even within the complex environment of an enzyme. We further examine how this disparity varies with the local tyrosine environment and discuss its potential implications for biological function.

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FDET eigenvalue equations for a new class of applications

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Frozen-Density Embedding Theory (FDET) concerns the constrained minimisation of the Hohenberg-Kohn energy functional $E_v^{HK}[\rho]$:

$$\min_{\substack{\rho \rightarrow N_{AB} \\ \forall \mathbf{r} \rho(\mathbf{r}) \geq \rho_{N_B}(\mathbf{r})}} E_v^{HK}[\rho] = \min_{\rho_{N_A}} E_v^{HK}[\rho_{N_A} + \rho_{N_B}] = E_v^{HK}[\rho_{N_A}^o + \rho_{N_B}]. \quad (1)$$

In practice, the minimisation is performed by solving an eigenvalue equation [1] resembling the one used in conventional QM/MM methods for embedded N_A electrons. In contrast to QM/MM, a universal density bi-functional is used for the embedding potential $v_{emb}^{FDET}[\rho_{N_A}, \rho_{N_B}]$ instead of system dependent parameters. The FDET eigenvalue equation is used in various multi-level simulations of species in condensed phase in several research groups. FDET also provides the expressions for the total energy for variational and non-variational methods of Quantum Chemistry treatments of electron-electron interactions consistent with the Hohenberg-Kohn energy functional.

So far, the most successful applications of FDET eigenvalue equation concerned cases where the electrons are localized in *a priori* known region of the total system (embedded chromophore for instance). This limitation is caused not by FDET itself but by the approximation: $v_{emb}^{FDET}[\rho_{N_A}, \rho_{N_B}] \approx \tilde{v}_{emb}^{FDET}[\rho_{N_A}, \rho_{N_B}]$. Recently, we demonstrated that the FDET eigenvalue equation can also be used for modelling systems in which the redistribution of electron density between the embedded subsystem and its environment is not known *a priori* [2, 3]. This is achieved through the use of an approximant for the kinetic component of $v_{emb}^{FDET}[\rho_{N_A}, \rho_{N_B}]$ which takes into account its asymptotic behavior in regions where $\frac{\rho_{N_A}(\mathbf{r})}{\rho_{N_B}(\mathbf{r})} \ll 1$ [4].

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Poster Abstracts

Influence of Water Models on Protein–DNA Interactions: A Comparative Study

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This study compares commonly used water models with the TIP4P-D model, which was developed to provide a more accurate description of nonpolar interactions, and to evaluate how this correction influences protein–DNA complexes. Molecular dynamics simulations of these complexes were performed to assess their structural stability, with a primary focus on stability of native and formation of new non-native protein–DNA contacts. The results indicate that while the use of TIP4P-D does not significantly affect overall complex stability, it exerts a (desirable) strong destabilizing effect on individual hydrophobic contacts formed during the simulations. This suggests that the TIP4P-D model provides a more realistic representation of hydrophobic interactions within protein–DNA complexes, which is consistent with its behavior previously observed in simulations of isolated proteins.

Structure Analysis of Ternary Complex of Pt(II) Metallodrugs and Cucurbituril CB[8]

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Monofunctional Pt(II) coordination compounds are investigated as a potential alternative of anticancer metallodrugs.[1] The encapsulation into macrocyclic carries decorated with suitable vector appears to be a possible strategy to increase specificity of action and to protect prodrug from premature activation. In this context pH of medium can strongly affect composition of Pt coordination sphere and mode as well as affinity of the binding into cavity of a carrier.

In this contribution NMR study of binding equilibria between cucurbituril CB[8] and two equivalents of $[\text{Pt}^{2+}(\text{NH}_3)_2(4\text{-Ph})\text{Py}\mathbf{X}]$ ($\mathbf{X} = \text{Cl}^-$, OH^- , H_2O) will be presented. We have systematically monitored process of transition from *anti* to *syn* arrangement of Pt compounds as a function of pH, Cl concentration and character of an organic anchor. The NMR experiments are interpreted using molecular modelling and DFT calculations of induced chemical shifts. Our recent findings indicate that lower pH and Cl ligand partially inhibit transformation of antiparallel orientation in this type of ternary complexes.

Acknowledgements: This work was supported by the Czech Science Foundation (GA24-10760S).

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Comparing RESP-Based Approaches for Deriving Partial Charges in Biomolecules

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Electrostatic interactions are a key determinant of biomolecular structure, dynamics, and molecular recognition, making their accurate representation essential for reliable molecular dynamics simulations. In contemporary fixed-charge force fields, atomic partial charges are commonly derived using the Restrained Electrostatic Potential (RESP) method. Although RESP has become the standard approach for biomolecular force field parameterization, its reliance on single-conformation gas-phase electrostatic potentials and restrained fitting can limit its ability to describe conformationally dependent electrostatics, and account for condensed-phase polarization effects. These limitations have motivated the development of improved RESP-based methodologies, including Multi-RESP, W-RESP, and RESP2, which incorporate ensemble-based fitting strategies, refined restraint schemes, and enhanced electrostatic models.

In this work, we systematically evaluate RESP, Multi-RESP, W-RESP, and RESP2 for deriving atomic partial charges in biomolecules. The resulting charge models are compared with the library charges employed in current biomolecular force fields to quantify how methodological differences in electrostatic potential fitting, restraint schemes, conformational averaging, and solvent treatment influence the resulting electrostatic parameters. The study provides a comprehensive assessment of contemporary RESP-based methodologies and identifies promising directions for improving electrostatic parameterization while preserving compatibility with established fixed-charge force fields.

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Combined QM/MM Description of Electron Transfer Between Coenzyme FAD and diCys Redox Center of TrxR

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The theoretical study focuses on the proton transfer mechanism within the active site of thioredoxin reductase 1 (TrxR1). To determine energy barriers and verify the reaction mechanism, we used hybrid QM/MM simulations and Steered Molecular Dynamics (SMD) at both semi-empirical (PM7) and Density Functional Theory (DFT) levels. The results showed that the originally proposed path via the Cys 50 residue is energetically unfavorable. However, we identified a thermodynamically preferred path involving direct transfer to Cys 55, which is stabilized by the enzyme's environment. The thesis also analyzes the methodological limitations of non-equilibrium dynamics, specifically the thermodynamic paradox, contributing to more accurate modeling of enzymatic reactions.

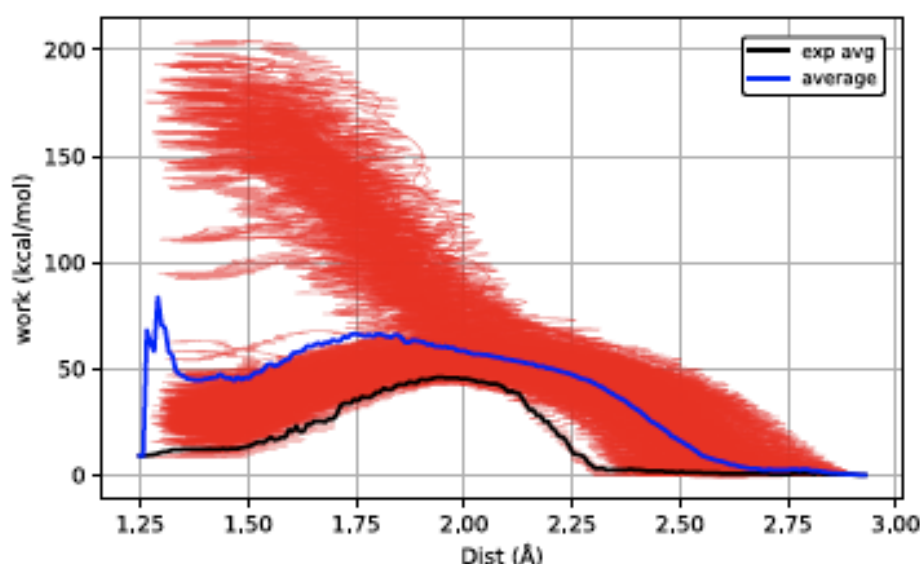


Figure 1: DFT energy profile for one of the chosen mechanisms of proton transfers from SMD simulation.

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Machine Learning in RNA Atomistic Simulations

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In this work the results of the dataset construction and specialized RNA/DNA SpookyNet [1] model training and testing are reported. The dataset in the current version consists of 466 059 datapoints; both bottom-up (small, hydrogen-saturated fragments of molecules) as well as top-down structures (dinucleotides with up to 8 water molecules, water clusters etc.).

Method	Nuc. Conformations [kcal/mol]	Nuc. WC pair conformations [kcal/mol]	ACxGU (vacuo) [kcal/mol]	ACxGU (explicit water) [kcal/mol]
Ensemble 1	0,383	0,532	1,414	1,258
Ensemble 2	0,433	0,429	1,335	1,571
Ensemble 3	0,338	0,555	1,216	0,994
B3LYP D3BJ	0,81	1,59	1,58	4,25
TPSS D3BJ	2,2	2,92	3,72	6,03

Figure 1: Relative conformational energies for selected test cases in different methods.

The models have been tested on both absolute and relative energy errors vs the reference method (ω B97M-V, def2-TZVP) and other methods: DFT functionals B3LYP and TPSS, both with def2-TZVP and D3-BJ corrections. The ML approach has shown remarkable consistency with the ref. method, showing absolute errors of 0.1-1 meV/atom. It has also performed better than both DFT test functionals in relative energy comparisons, with much faster single-point calculation times (2-5 orders of magnitude).

The models have also been tested in optimization tasks with the self-written ASE implementation of GBSA implicit solvation model. It has been tested for systems with four nucleosides, either as single strand or 2x2 systems. The RMSD for such tasks fell between 0.1 - 0.5 Å, while being 5-6 orders of magnitude faster than the ω B97M-V optimizations with CPCM solvation scheme.

Acknowledgements: Results have been acquired in NCN grant no.2022/46/E/ST4/00377 of dr hab. Rafał Szabla. Calculations were performed at the Wrocław Centre for Networking and Supercomputing.

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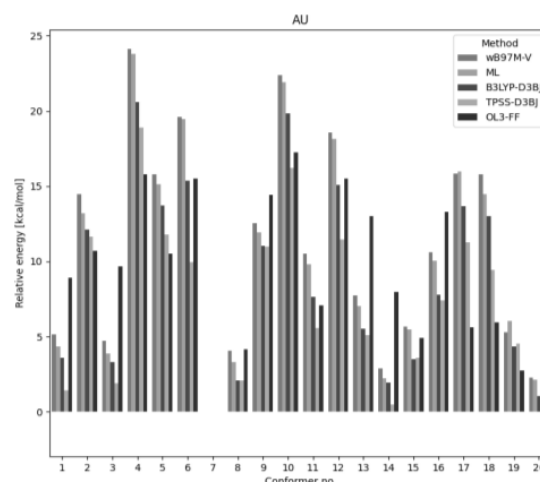


Figure 2: Relative conformational energies for AxU Watson-Crick pair in different methods.

Paracetamol Adsorbed into Metal Organic Framework MIL-140C

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Metal–organic frameworks belonging to the MIL-140 family [1] exhibit high structural stability and possess approximately 10 Å channels, making them promising materials for drug delivery applications. In this study, the encapsulation of paracetamol within MIL-140C was investigated using a combination of computational modelling and experimental methods. Molecular simulations indicated that, among nine investigated compounds, paracetamol showed the most favorable energetic interaction with the framework. The calculations further suggested an optimal loading of four paracetamol molecules per unit cell, facilitated by cooperative hydrogen-bonding interactions. MIL-140C was prepared using a solvothermal synthesis route, and its phase purity was verified by powder X-ray diffraction. Optimization of the synthesis demonstrated that the water content of dimethylformamide plays a crucial role in determining phase purity, with MIL-140C formation achieved only when semi-dried dimethylformamide was used. The drug-loading procedure was subsequently optimized by evaluating different solvents, with chloroform providing the most suitable environment. A mild washing procedure was found to be necessary to avoid collapse of the framework structure. Argon physisorption measurements supported successful paracetamol incorporation, as indicated by a 49.7% decrease in micropore area at the highest loading level. Additional characterization using FT-IR spectroscopy, SEM, and EDX further confirmed the presence of paracetamol within MIL-140C. Although the computational model involved several simplifications, including a rigid framework and the omission of solvent effects, the simulations proved effective in directing the experimental strategy. Overall, the results demonstrate the potential of MIL-140C as a carrier for paracetamol delivery and highlight the benefits of integrating molecular simulations with experimental characterization to investigate host–guest interactions in MOF-based materials.

Acknowledgements: Support from the Grant Agency of the Czech Republic No. 25-16442S is acknowledged.

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Modeling Host-Guest Interactions of B₁₈H₂₂ and Cyclohexane in MOFs Using the Hybrid QM/MM Approach

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While classical molecular dynamics (MD) simulations - especially when combined with X-ray or electron diffraction - are powerful tools for resolving crystal structures, their accuracy is fundamentally limited by the underlying force fields. To bypass these limitations and capture the precise interactions between guest molecules and a host metal-organic framework (MOF), a hybrid quantum mechanical/molecular mechanical (QM/MM) approach can be utilized.

In this contribution, we focus on arrangement of cyclohexanes and B₁₈H₂₂ clusters in the well-established prototypical Fujita MOF [(ZnI₂)₃(tpt)₂][1] (tpt = 2,4,6-tris(4-pyridyl)-1,3,5-triazine). Based on optimized geometries obtained from quenched molecular dynamics using the Dreiding force field, the individual adsorbed molecules along with proximal atoms (up to the distance of ca 8 Å) were included into the QM part. The wave function was polarized by atomic charges from the outer region using electronic embedding and total energies were evaluated within the subtractive scheme utilizing several density functional theory (DFT). Optimizing the QM region, refined structures and positions of guest molecules were obtained. Binding energies of B₁₈H₂₂ cages and cyclohexanes in the system along with non-covalent interactions and flexibility of the MOF scaffold were analysed. Simultaneously, this technique provides access to electron densities of guest molecules.

In summary, we employ this well-defined system to investigate the potential and limitations of combining our approach with single-crystal X-ray diffraction to improve the precision of structural determination.

Acknowledgements: This work is supported by the Czech Science Foundation (grant no. 25-16442S).

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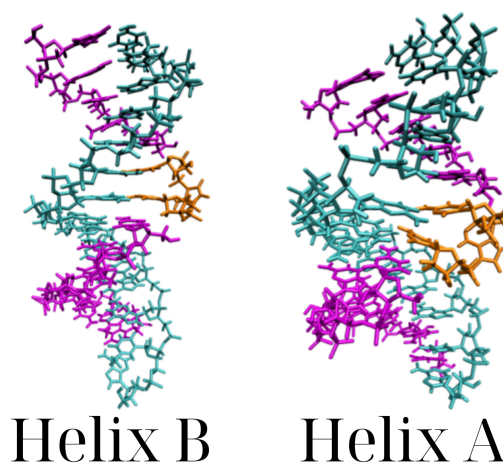
A-type Helicity Controls Efficient Nonenzymatic Template Copying of Nucleic Acids

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Nonenzymatic RNA primer extension has been investigated for almost five decades, with numerous studies indicating that imidazolium-activated dinucleotides are important intermediates in this process. These observations contribute to the view that RNA may have played a fundamental role in the emergence of life [1–3]. In comparison, nonenzymatic DNA self-replication is considerably less efficient and therefore appears to have had limited relevance under prebiotic conditions, although it remains of interest as a possible route for DNA synthesis. Current DNA synthesis methods, including solid-phase synthesis and PCR, are well established but are associated with several limitations, such as complex procedures, the need for costly enzymes, and substantial solvent consumption. Recent experimental results have further shown that DNA synthesis is considerably more efficient when an RNA molecule is used as the template rather than DNA, which may be related to the characteristic A-form helical structure of RNA [5].

Here, we investigate nonenzymatic DNA self-replication on an RNA template using classical molecular dynamics simulations and phosphoroimidazole activation. Our results demonstrate that the RNA template promotes an A-type helical conformation in the resulting DNA/RNA hybrid duplex, unlike the B-type structure typically observed in DNA/DNA duplexes. Structural analysis indicates that the helical conformation of the duplex is a key determinant of the efficiency and feasibility of nonenzymatic primer extension.



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Pseudocontact NMR Shifts in Transition-Metal Compounds and Their Supramolecular Complexes

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Paramagnetic NMR spectroscopy (pNMR) is a powerful tool in the studies of open-shell systems. Hyperfine interactions between unpaired electrons and observed nuclei produce long-range perturbations causing significant signal broadening and large shifts of NMR signals compared to their diamagnetic analogues.

Ru(III) and Os(III) compounds (examples shown in Fig. 1A) and their host-guest complexes with cucurbit[7]uril (Fig. 1B) exhibit promising migrastatic and cytotoxic effects, making them attractive candidates for development of anticancer metallodrugs. The objective of this work is the calculation and interpretation of pseudocontact shifts in novel Ru(III) and Os(III) compounds and their host-guest complexes. Quantum chemistry calculations are employed to characterise their electronic structure and to elucidate the binding modes of the metallodrugs to macrocyclic carriers such as cucurbit[7]uril.

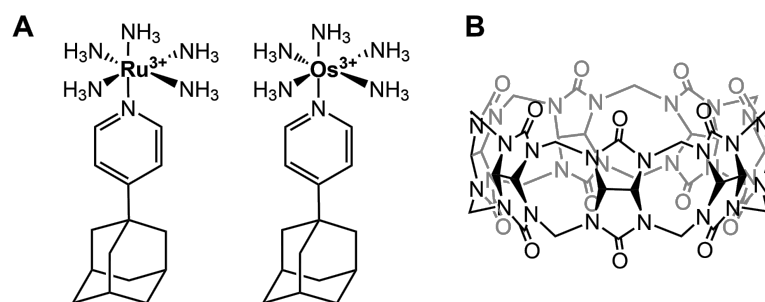


Figure 1: A) Examples of studied Os(III) and Ru(III) compounds. B) Structure of cucurbit[7]uril.

Acknowledgements: This work has received support from the Czech Science Foundation (24-10760S). Viliam Volko is a Brno Ph.D. Talent Scholarship Holder – Funded by the Brno City Municipality.

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Simulation of Electron Transfer on Biomolecular Bridges by Non-Adiabatic Molecular Dynamics

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Molecular electronics uses (bio)organic molecules and organometallic complexes as components of electronic devices, enabling applications such as highly sensitive biosensors. Advancing these technologies requires understanding electron transport, molecular structure, and their dynamics through quantum calculations and molecular dynamics simulations. Accurate modeling remains challenging because of the interaction between molecular and metallic electronic states, as well as the influence of thermal motion, vibrations, and non-adiabatic electron transfer. Consequently, realistic simulations must explicitly couple electronic and nuclear dynamics.

In this work, we employ non-adiabatic molecular dynamics (NAMD) with the Fewest Switches Surface Hopping (FSSH) method [1] to simulate electron-transfer processes in model molecular bridges. The simulations are performed using the open-access LIBRA modular library [2], which enables not only the simultaneous propagation of nuclear motion and the population of the related electronic states, but also state-of-the-art modifications and developments needed for the treatment of heterogeneous molecule/metal interfaces. We demonstrate the feasibility of these calculations on several model systems, ranging from Tully's models [1] to small rigid molecules treated under the neglect-of-back-reaction approximation (NBRA) to atomistic junction models based on benzene-1,4-diamine (BDA) and benzene-1,4-dithiolate (BDT) molecules. These methodology benchmarks and developments are presented in the context of intended applications on complex biomolecular electronic devices based on redox proteins that are investigated in our group.

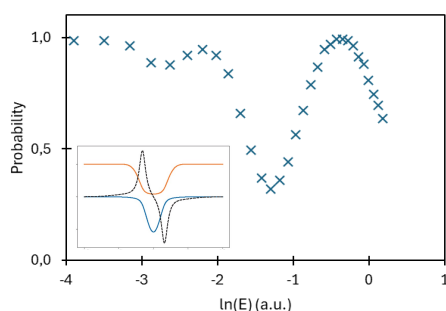


Figure 1: Computed transmission obtained by FSSH on Tully's DAC model

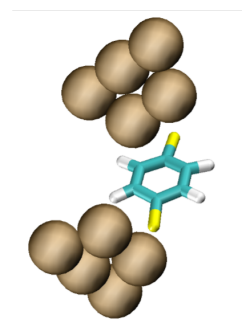


Figure 2: Atomistic model of BDT bridge.

Acknowledgements: This work was supported by Czech Science Foundation (Project 25-16698S)

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Interactions of Ultra-Fine Polystyrene Nanoparticles with Lung Surfactant Monolayers and Bilayers: A Combined Molecular Dynamics and Experimental Study.

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Nowadays dangerous air pollutants are omnipresent and have negative influence on living organisms. The most vulnerable part of human body to air pollutants are lungs, especially lung surfactant (LS). [1] It has been recognized that substances that penetrate the alveolar space may interact with LS and perturb its functioning. Common pollutants gaining recognition in recent years are polymers such as e.g. polystyrene (PS). This study investigates the pollution by different size PS molecules of pulmonary surfactant from a computational perspective, in correlation with experimental data. The research focuses on the pulmonary surfactant lipid monolayer and bilayers, which serves as the body's first natural barrier in the respiratory process. We employed a series of membrane models composed of four monolayers DPPC:POPC and DPPC:POPC:POPG:CHOL in 1:1 and 10:5:3:2 molar ratios, respectively, as well as DPPC:POPC:POPG:CHOL 10:5:3:2 for bilayers. The PS models with 20, 50, and 90 repeat units were generated. These chain lengths correspond to MW of 2085, 5209.5, and 9375.5 g·mol⁻¹, respectively. All models were constructed using the CHARMM-GUI interface and calculations were performed in Gromacs 2022 software and visualized in VMD software. A key objective of the study is to assess interaction of ultra-fine PS nanoparticles with lung surfactant model systems by MD simulations and complementary experimental data. PS rapid incorporation disturbs LS functionality by decreasing its fluidity and influencing lipid composition near PS nanoparticles.[2]

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Calculating resonance Raman optical activity for transition metal complexes: importance of explicit solvation

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Spectroscopy of Raman optical activity (ROA) is a chiroptical technique derived from Raman spectroscopy. ROA is particularly useful for studying molecular conformations of chiral molecules in solution, namely pharmaceutically active substances, sugars, peptides, and other biomolecules. However, the signal is often weak, requiring long acquisition times. One way to increase the signal is the absorption of the excitation frequency (i.e. resonance) by the sample. The technique is then called resonance ROA (RROA) [1-2]. It is still a relatively novel technique that lacks a reliable computational protocol needed for the interpretation of experimental spectra.

We analyze RROA spectra of four resonating transition metal (Co^{3+} , Cr^{3+} , Ni^{2+} , Cu^{2+}) complexes with a small (EDDS) chelating ligand. Simulation of resonance Raman and ROA spectra was done by density functional theory (DFT) and subsequent numerical differentiation of sum-over-states polarizabilities. The far-from-resonance contribution is also examined. The accuracy of implicit and explicit solvation regimes is compared.

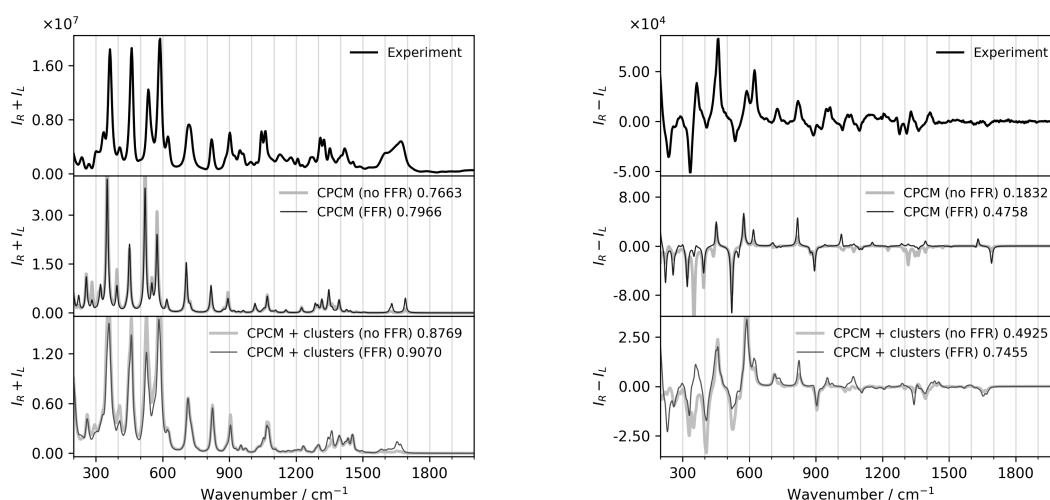


Figure 1: Experimental and simulated resonance Raman (left) and ROA (right) spectra of Co(III)EDDS, the similarity indices of the calculation with the experiment are also shown

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Computational and QM/MM Study of Galactofuranosyltransferase GlfT1 of *Mycobacterium tuberculosis*

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Tuberculosis is a global health emergency caused by the critical-priority pathogen for research and development, *Mycobacterium tuberculosis*. The bacterium's unusually hydrophobic cell wall endows it with a remarkable resistance to the outside environment, including common antibiotics. [1] The galactan core of the cell wall is an essential structure responsible for its structural stability which has no human homologue. Consequently, its biosynthesis represents an attractive pharmacological target for the development of new anti-tuberculosis drugs. [2]

GlfT1 is a key enzyme of the galactan pathway that initiates its biosynthesis by transferring a galactofuranosyl moiety to a glycolipid acceptor substrate. [3] Unfortunately, much is unknown about the enzyme, including its structure and reaction mechanism.

Employing AlphaFold 2, [4] we first obtained a suitable model for docking simulations. Since docking using conventional methods failed, we instead designed a simulated annealing methodology with carefully selected distance restraints to position both substrates into their respective binding sites. The obtained pre-reaction complexes were then subjected to explicit solvent molecular dynamics simulations. Next, using a hybrid QM/MM methodology with free energy calculations, we used the most stable pre-reaction complex to simulate the GlfT1 transferase reaction. Here, we present the structure of the pre-reaction complex, including a characterisation of the tentative interactions in the active site, and the results of our QM/MM simulations.

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Evaluation of DNA Force Fields: A/B Conformational Equilibria, Sugar Puckering, and Water Model Effects

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Accurate modeling of DNA conformational equilibria remains a key challenge in molecular simulations. The balance between A- and B-DNA forms, closely linked to sugar pucker, is essential for processes such as protein–DNA recognition and the stability of DNA/RNA hybrid duplexes. However, commonly used force fields often exhibit systematic biases in this equilibrium, which can affect conformational sampling and the behavior of biomolecular complexes.

Here, we present a systematic assessment of selected current DNA force fields with respect to their ability to describe sugar pucker and the A/B conformational equilibrium in canonical DNA duplexes, DNA/RNA hybrids, and protein–DNA complexes. Our results show that a recently introduced parameter set (OL24) [1] significantly improves the description of the A/B equilibrium by shifting it toward a more realistic balance and increasing the population of A-like conformations, while maintaining an accurate representation of canonical B-DNA.

In addition, we evaluate the impact of different explicit water models on canonical DNA duplexes, focusing on selected conformational equilibria and structural features, including A/B balance and terminal fraying. Our results demonstrate that both force field parametrization and solvent representation play a critical role in determining these properties and should therefore be carefully considered for reliable modeling of DNA structure and dynamics.

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