HPC ECHO

From science to innovation

2022-2023

Content

Foreword

Dr. Endre Spaller

President

KIFÜ has more than 21 years of experience in operating supercomputers.
After Leo and Apollo, earlier this year we handed over Komondor, so far, the most powerful supercomputer in Hungary and its region. The Komondor was the largest domestic IT development of the decade, and there is great interest in its use. I am proud that we have already had a cooperation agreement with 12 higher education institutions, 67 SMEs and 1 large corporation to use the supercomputer. Our 5 petaflops machine has already been used by researchers during the pilot period. There are a good number of outstanding scientific results that cannot be ignored. You can read about them in this year's HPC Echo.

Krisztián Kongó

Vice-President responsible for Infrastructure

The Komondor is not only the most powerful supercomputer in our country, but also the 21st greenest supercomputer in the world today, with a wide range of applications. From the simulation of attosecond processes, through the development and application of pharmacoinformatics methods, to the investigation of environmental and health risks from micro- and nanomaterials, it has been used by researchers in a number of outstanding scientific projects. In the third issue of Echo, we present ten of these projects, which are of great value and interest.

AGRONOMICS **BIOLOGY** **CHEMISTRY** **PHYSICS**

Identification of quantum bit candidates in topological superconductors

Perhaps it is not an exaggerated claim that the impoact of semiconductor-based information technology on civilization can only be compared to the wheel and the steam engine. Although various numerical tasks can be solved efficiently (i.e. with polynomial scaling) using classical computer, many practical problems (e.g. pharmaceutical active substance modeling) are solved with exponential scaling. Transistors, which function as switches in classical computer architectures, perform operations on a series of bits encoded with a two-state electrical signal (voltage/current). Using quantum superposition and entanglement, quantum problems can be solved with polynomial instead of exponential scaling in a quantum bit-based computational representation. The promise of this revolutionary speed increase drives one of today's most exciting research ventures, the foundation of quantum computing technology. The complexity of the topic is clearly demonstrated by the fact that the efficient physical implementation of quantum bits is an area of active research to this day.

In one of the most promising model architectures, the quantum bits are represented by the zero-energy elementary excitations of superconductors, called Majorana fermions, characterized by a band structure with a non-trivial topology, resistant to environmental disturbances. Although these excitations are excellent for storing quantum information, they cannot be used for universal operations (e.g. gates that generate entanglement). It has been demonstrated that a larger set of quantum operations can be performed with the help of parafermions, which can be regarded as generalized Majorana fermions stabilized by interactions.

In the literature, parafermionic systems are typically studied using either approximate, field-theoretic methods, or they are investigated in complicated, unfeasible microscopic models derived from so-called clock models.

Members of the research group: Gergely Barcza, László Oroszlány, Botond Osváth

On the research group

Gergely Barcza obtained his doctorate in physics at ELTE. As a postdoctoral fellow, he worked at the J. Heyrovsky Institute in Prague and at the Wigner Physics Research Center. He is currently a senior scientific associate at the latter institution, where he studies correlated electron systems.

László Oroszlány received his doctorate in physics at Lancaster University in England. After a postdoctoral period at ELTE and BME, he has been lecturing at ELTE since 2014. His research focuses on numerical solid-state physics, especially on the theoretical investigation of topological insulators.

Their joint PhD student, Osváth Botond, performed a significant part of the numerical calculations in the project, and is currently a postgraduate at the ELTE Doctoral School of Physics.

In our project, we investigated a novel, experimentally relevant topological quantum system in which parafermionic excitations are expected to appear. The computation-intensive numerical modeling tasks were performed on the KIFÜ supercomputer system.

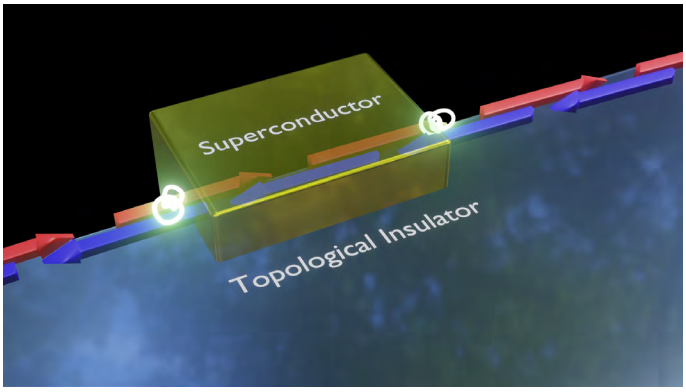

Figure 1: *Schematic plot of the investigated solid-state physics system. In the presence of interactions, low-energy excitations more complicated than Majorana fermions emerge at the interface of a topological insulator and a conventional superconductor.*

As Figure 1 illustrates, the phenomena to be investigated are basically determined by the contact surface of the topological insulator-superconductor domains, so our goal was to construct and numerically investigate a relatively simple quantum model that is experimentally feasible and is able to describe the topological insulator edge states. In our microscopic lattice model, the localized electrons can move along the lattice points of a ladder structure, whose behavior is significantly influenced not only by the spin-spin interaction, but also by the superconducting interface. Through competitive interaction processes, by tuning the parameters characteristic of our model (for example: chemical potential, spin-spin interaction, superconducting potential), the system can exhibit completely different phases.

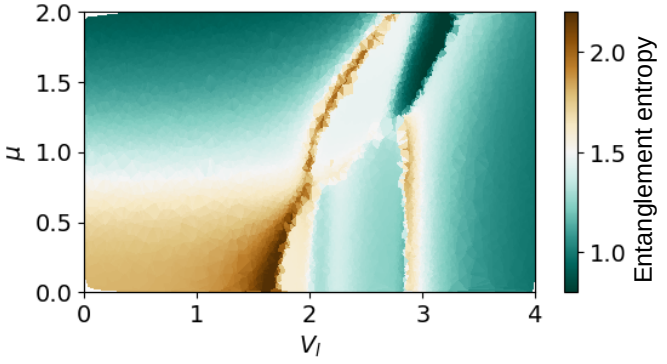

Figure 2: *Phase diagram as a function of interaction strength and chemical potential. The entanglement entropy, which can be interpreted as the average of all possible multi-electron correlations, can be used to distinguish phases with different features.*

This can also be observed in Figure 2, where the sharp changes visible in the coloring indicate the border of the different phases. In our work, we studied the properties of the model mainly by varying the chemical potential and the strength of the interaction. The main interesting feature of the model is that for parameters wedged between the usual metallic and insulating phases (around VI=2.5), we also identified a phase with a fourfold ground state degeneracy, which states are localized at the interface of the insulating and superconducting regions. In this interesting parameter range with finite degeneracy, we also studied the Josephson effect. Note that the precise numerical investigation of this low-energy modulation phenomenon was challenging. The 8π periodicities observed for the localized edge states in our calculations confirm the expected parafermionic behavior.

Further details of the system, which is also experimentally feasible and can potentially be used as a programmable quantum bit, are currently being investigated.

The structural mechanism of function of G protein-coupled receptors

G protein-coupled receptors (GPCRs) are located in the plasma membrane that defines the boundary of cells and act as transmitters of cell-cell communication. These proteins relay signals received from the surroundings towards the inside of the cell. These signals are special molecules secreted by other cells which then localize with and bind to the receptors. The list of such molecules, often referred to as ligands, include hormones, pheromones, odorants, light sensitive molecules, neurotransmitters to name a few. Binding of a ligand to a GPCR initiates a cascade of events inside the cell. The first, universal step of such signaling cascades is the activation of G proteins. Basic physiological processes that are regulated by GPCRs include for example vision, the sense of smell and taste, cardiac rhythm and pain sensation. GPCRs can be activated or blocked by drug molecules delivered to the body from external sources, providing an opportunity for the treatment of various diseases and abnormalities. Approximately 30% of the commercially available prescription medications exert their action through binding to GPCRs, which makes them one of the most important target protein family of modern drug development. [1] Deeper understanding of the functional mechanism of these receptors is essential for the design of more potent medications with less side effects.

The structure of GPCRs can be divided up to three main units: the extracellular region (outside the cell), the transmembrane domain (inserted in the cell membrane) and the intracellular region (inside the cell). In rhodopsin-like GPCRs the transmembrane domain is most responsible for signal transduction because both the ligand binding pocket and the G protein binding interface is found in this unit. The three dimensional structure of the transmembrane region is bundle of seven α-helices. According to the details of receptor activation revealed to this

Members of the research group: Dr. Attila Borics, Ádám Ködmön, Sarkar Arijit, Éva Tóthné Papp, Dr. Csaba Tömböly (currently abroad)

On the research group

Chemistry based research in our group is focused on the understanding of protein – small molecule interactions and structural mechanisms of protein function. The potential drug target opioid, cannabinoid, vasopressin and sigma receptors are investigated by spectroscopic, theoretical and in vitro methods to obtain structure – activity/function relatioships. Beyond the preparation of small molecules, peptides and proteins enriched in chemical information, i.e. stable isotopes, unnatural building blocks, fluorophores, radiactive labels, protein modification strategies are also developed for the preparation of membrane associated proteins.

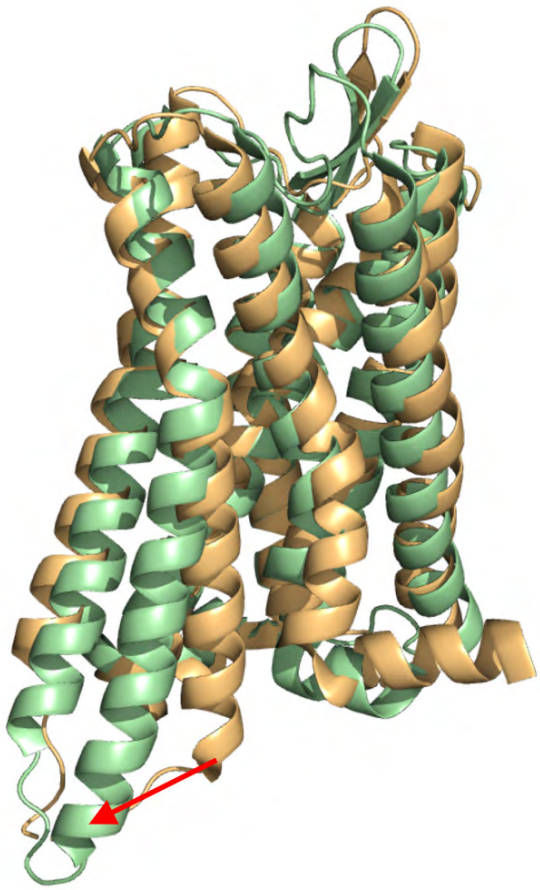

Figure 1: *The structure of the transmembrane region of the μ-opioid receptor in active (green) and inactive (orange) state. Red arrow indicates the horizontal disposition of the 6th transmembrane helix upon activation.*

date, the activation of the receptor is manifested in the horizontal disposition of the 6th transmembrane helix. (Figure 1)

According to a recent, widely accepted hypothesis the structure of the receptor could be classified as an ensemble of dynamically interconverting active, intermediate and inactive structural states and the binding of an activating ligand increases the population of the active states. [2] Another proposal states that structural rearrangements leading to receptor activation takes place through the consecutive activation of so-called structural microswitches, generally located in the transmembrane region. [3]

Our research group have complemented the above theories with a new hypothesis which, apart from the structural and dynamic properties, highlights the importance of electrostatic charge distribution inside the receptor. The hypothesis states that ligand binding temporarily tips the electrostatic balance in the transmembrane region, which is then neutralized through minor structural rearrangements and a charge shift towards the intracellular surface of the receptor, leading to G protein dissociation and activation. (Figure 2)

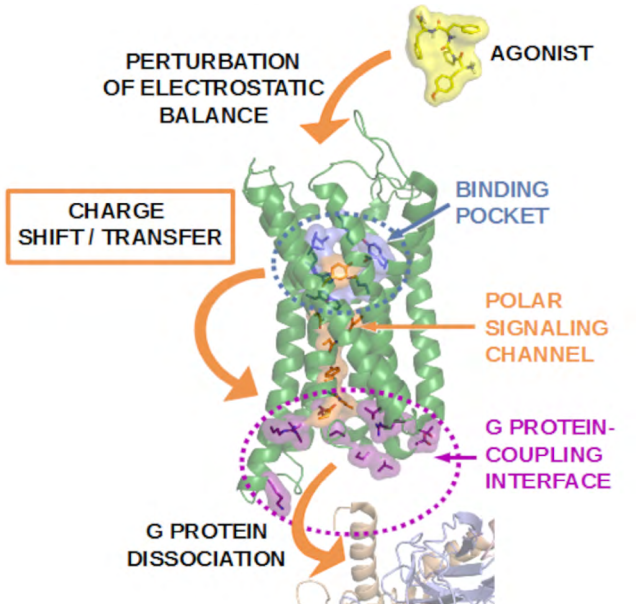

Figure 2: *Auxiliary hypothesis of the activation mechanism of class A G protein-coupled receptors.*

The plausibility of the above hypothesis was investigated through large scale molecular dynamics simulations of the μ-opioid receptor (MOP), the β_2 adrenergic receptor (β_2AR) and the type I cannabinoid receptor (CB1) using the Debrecen2 supercomputing facility supplied by KIFÜ.

During mulecular dynamics simulations dynamic changes of receptor-ligand interactions have been assessed, and their effects on the receptor structure. Thorough analysis of our results led us to identify a so-called polar signaling channel connencting the ligand binding pocket and the intracellular G protein binding interface of the receptors. [4-6] This channel is formed by evolutionally conserved polar amino acids in case of all three receptors, which perform synchronous movements in the ligand- and G protein-bound active state receptors. On the other hand, such concerted motions were not obseved in the inactive state receptor or in the absence of ligands or G proteins. These observations partially confirm our theory, suggesting that the shift of electrostatic balance that accompany receptor activation is transmitted through the syncronous movements of the polar signaling channel in the transmembrane region.

The assumptions drawn from our simulation results were further tested in experiments. First, the polar signaling channel of the MOP receptor was modified using molecular biology techniques in order to alter the electrostatic balance of the channel. Preparations of cells expessing these modified proteins have been then subjected to receptor binding and functional tests. For all modified receptors, loss or significant decrease of ligand binding and G protein activation was observed. The ligand binding capacity of modified MOP receptors was tested utilizing a newly developed NMR spectroscopic technique (Saturation Transfer Triple Difference, STTD) in live cellular samples. These measurements have confirmed our observations taken previously in the pharmacological examinations. Molecular dynamics simulations of the modified receptors were also performed in parallel with the experiments. In agreement with the experimental results, synchronous movements of the previoulsy identified polar signaling channel, associated with receptor activation, were not observed in the modified receptors.

The results presented here may contribute to the better understanding of the general function of GPCRs and to the development of novel active substances with improved clinical properties. The research strategy applied here could be applied for the investigation of other biological systems of medical relevance and provide a foundation for the development of modern, targeted therapeutic agents.

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[2] Latorraca, N.R.; Venkatakrishnan, A.J.; Dror, R.O. GPCR Dynamics: Structures in Motion. Chem. Rev. 2017, 117, 139–155.

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[6] Sarkar, A.; Mitra, A.; Borics, A. All-Atom Molecular Dynamics Simulations Indicated the Involvement of a Conserved Polar Signaling Channel in the Activation Mechanism of the Type I Cannabinoid Receptor Int. J. Mol. Sci. 2023, 24, 4232.

Exploration of an RNA modifying mechanism and the investigation of its potential therapeutic application

The epigenetic modification of DNA (i.e., modifications not affecting the nucleotide sequence) has been a field of intensive research for decades. The analogous changes in the RNA sequences are called epitranscriptomic modifications. These modifications may also have significant effects on cell function and gene expression, no wonder the epitranscriptomic investigation of RNAs has become such a widely investigated field lately.

The uridine to pseudouridine transformation is the most abundant post-transcriptional modification of RNA. This reaction is catalyzed not only by stand-alone pseudouridine synthase enzymes, but also by a large protein-RNA complex called box H/ACA pseudouridine synthase shown in Figure 1. Mutations affecting the protein components of this complex are often linked to serious illnesses like bone marrow failure, cancer, or nephrotic syndrome.

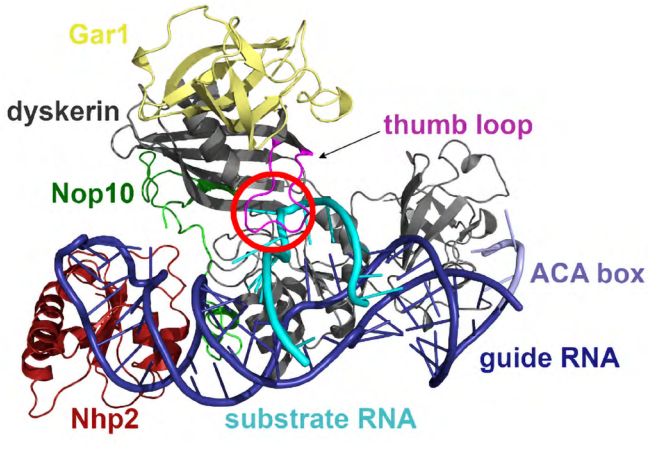


Figure 1: *Structure of the box H/ACA pseudouridine synthase. The active site is indicated by a red circle.*

Members of the research group: Dóra Judit Kiss, Julianna Oláh, Gergely Tóth, Máté Varga, András Stirling, Dóra Karancsiné Menyhárd, György Ferenczy

On the research group

Dóra Judit Kiss works as a research fellow in the Medicinal Chemistry Research Group of the HUN-REN Research Centre for Natural Sciences. Her research interest includes the investigation of enzyme reactions with QM/MM calculations and drug design and modelling on GPCR targets.

Julianna Oláh is an associate professor in the Department of Inorganic and Analytical Chemistry at the Budapest University of Technology and Economics. Her research focuses on the computational investigation of the structure and reactivity of enzymes and of transition metal compounds.

Gergely Tóth (1966), assoc. prof. Institute of Chemistry, Loránd Eötvös University, Budapest. Research field: multivariate data analysis in chemistry, chemometrics, molecular simulations. Teaching activity: numerical methods in chemistry, multivariate statistics, computational chemistry. Author or co-author of 60 scientific publications. Máté Varga is an Associate Professor at the Department of Genetics of ELTE Eötvös Loránd University, where his research group investigates the etiology of monogenic human diseases using animal models. As part of this work, they have created and characterized a dyskerin loss-of-function zebrafish mutant recently.

Andras Stirling is scientific advisor at the Institute of Organic Chemistry of HUN-REN and professor at the Eszterhazy Karoly Catholic University. His research activities focus on the study of reaction mechanisms using computational chemistry tools, such as quantum chemistry, molecular dynamics and machine learning.

Dóra K. Menyhárd is a member of the HUN-REN-ELTE Protein Modelling Research Group, working at the Laboratory of Structural Chemistry and Biology at ELTE. She investigates structure-function relationships of macromolecular systems by theoretical and experimental methods, coupling quantum chemistry and molecular modelling calculations with protein structures determined mainly by crystallography and cryo-EM methods.

György G. Ferenczy is a scientific advisor at the HUN-REN Research Centre for Natural Sciences and the Semmelweis University. His research interest includes the development and application of computational methods to investigate biochemical and biophysical properties of extended molecular systems.

This system, with over 160,000 atoms was described with classical force field and the dynamics was investigated by molecular dynamic simulations using the KIFÜ infrastructure. In addition, we explored the mechanism of the uridine to pseudouridine transformation using a mixed quantum mechanical/molecular mechanical potential. The quantum mechanical method well describes the chemical transformation, and the molecular mechanics potential allows the inclusion of the effect of the extended protein-RNA complex. The use of this mixed potential made it possible to investigate the dynamics of the complex that turned out to be essential for a proper description of the process. It was found that the target uridine binds to the box H/ACA pseudouridine synthase in a distorted state that facilitates the subsequent uridine-pseudouridine transformation. It was also shown that mutant enzymes do not distort the uridine of the bound RNA, and this is in line with the experimentally observed inactivity of the mutants (Figure 2).

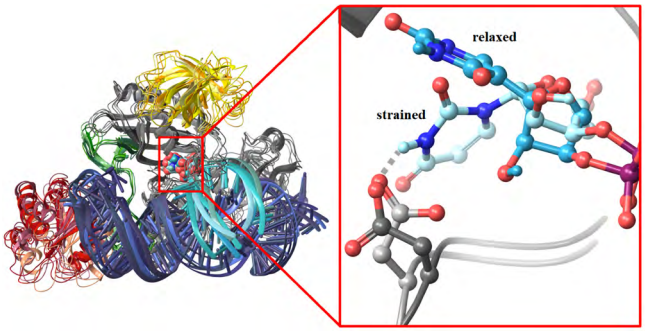


Figure 2: *Strained uridine bound to the wild type enzyme and relaxed uridine bound to an inactive mutant.*

The uridine to pseudouridine transformation starts with the dissociation of the uracil of the distorted uridine (S1 to S2 state in Figure 3). The uracil then rebinds with its C5 atom (S3 state) and a proton is transferred via a chain of water molecules (S4 state).

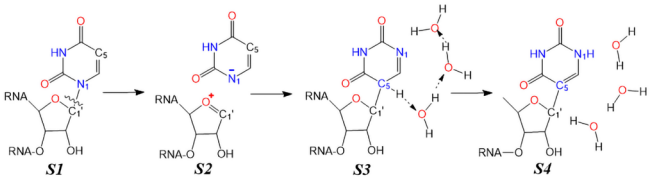


Figure 3: *Reaction mechanism of the uridine-pseudouridine transformation.*

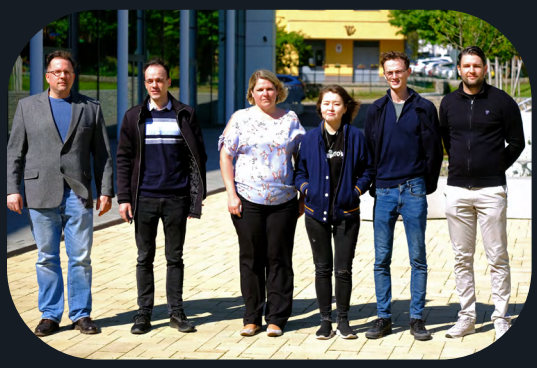
The above transformations are accompanied by a significant rearrangement of the enzyme environment; the partial opening of the protein binding pocket allows the formation of the water chain (S3 state) that mediates the proton transfer.

The above mechanism makes it possible to transform a uridine in any RNA that can bind to the guide RNA of the box H/ACA pseudouridine synthase, moreover, the structure of the guide RNA can be varied to a large extent. We proposed that engineered guide RNAs that can associate with the pseudouridine synthase complex may be applied to facilitate the pseudouridylation of nearly any substrate within the cellular transcriptome. This suggests the opportunity of programmable RNA editing and therapeutic applications for gene lesion-related diseases.

Development and application of pharmacoinformatics methods

Our Unit has been an active (core) user of the KIFÜ HPC service since the very beginning. Our research activity is focused on the development and application of computational methods applicable in drug design. The HPC infrastructure is of fundamental importance for us in both fields. Our Unit has received numerous prizes and academic awards for our above-mentioned activity strongly supported by the KIFÜ HPC service. Moreover, via KIFÜ, we have been granted computer resources in the PRACE DECI program providing access to the service of HPC servers of foreign countries.

In method development, we usually perform numerous, long probe runs to check the usefulness (validity) of the methods. Among our methods developed with the help of HPC, there are MobyWat (mobywat.com), Fragmenter (fragmenter.xyz), Wrap'n'Shake (wnsdock.xyz) for the precise calculation of target-drug interactions. During the COVID-19 pandemic, we developed a protocol HydroDock [1] that helps drug design on viral ion channels. In the case of drug binding to ion channels, water molecules play at least as important role as the target protein itself. Thus, ion channels proved to be particularly difficult targets from the viewpoint of drug design [2]. HydroDock provides the structure of the hydrated complex of protein-bound drugs just using the protein and drug molecules as input without other information. In this way, it solves the problem of "wet docking" (Fig. 1) which has been persistent for a long time. The method was successfully validated on the experimental structural data of the ion channel of inluenza A virus. Afterwards, we produced the atomic resolution structure of the hydrated complex of the SARS-CoV-2 ion channel (target in the fig.) with drugs of adamantane scaffold (ligand).



Members of the research group: Dr. Csaba Hetényi, Dr. Balázs Zoltán Zsidó, Dr. Rita Judit Börzsei, Bayartsetseg Bayarsaikhan, Magnus-Andrè Moritsgård, MD student, Viktor Szél, PhD student

On the research group

Dr. Csaba Hetényi is the Head of the Pharmacoinformatics Unit of the University of Pécs. He has has received numerous national awards including the Talentum Award, Bolyai Scholarship (twice), Bolyai Plaque, ÚNKP, Békésy Scholarship, Eötvös Scholarship. Co-inventor of US patents on antiretroviral therapy. Member of habilitation and doctoral committees, doctoral examiner, board member and associate editor of international journals.

Dr. Balázs Zoltán Zsidó, senior lecturer, graduated at the University of Pécs in 2019 as a pharmacist. He acquired his Ph.D in 2022 in neuropharmacology, his Ph.D. topic was the development and application of in silico drug design approaches. In 2021 he was awarded the Excellent Young Pharmacist Ph.D. student award, and in 2020 and 2021 he received the New National Excellence Project grants.

Dr. Rita Judit Börzsei, senior lecturer, graduated at the University of Pécs in 2006 as a pharmacist. She started working on computational molecular modelling in 2018 under the supervision of Dr. Csaba Hetényi. In addition to teaching and research, she places great emphasis on engaging students in science. Students under her supervision have won several awards at Student' Research conferences, New National Excellence Program of Hungary.

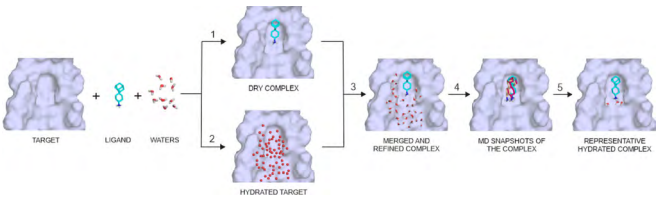


Figure 1: *The main steps of HydroDock protocol. A dry (1) and a wet (2) prediction branch are connected (3), after a molecular dynamics (MD) refinement (4), the protocol creates the hydrated complex structure (5) of the previously distinct molecules. The source of the figure: Zsidó et al. J. Chem. Inf. Model. 2021, 61, 8, 4011–4022, https://pubs.acs.org/doi/full/10.1021/acs.jcim.1c00488. (Further requests related to the figure should be addressed to the ACS publisher.)*

Besides development of methods another important research area of our Pharmacoinformatics Unit is the application of methods. During application the HPC resources are extensively utilized for the calculation of physiologically important biomacromolecules. These systems are membrane-embedded proteins, we investigate their dynamic movement in the presence of many explicit water molecules. These systems contain hundreds of thousand atoms (Figure 2.), we investigate their movement on a femtosecond scale, frequently for hundreds of nanoseconds each. This investigation can only be efficiently performed on HPC machines. The system on Figure 2 is the transient receptor potential cation channel, subfamily A (TRPA1) protein, which had an important role in the 2021 medicinal and physiological Nobel Prize. TRPA1 is an ion channel embedded in the membrane of human and animal cells. Its function is in the perception of pain, cold and itching. Furthermore, TRPA1 participates in the response to noxious environmental irritant stimuli, that evoke protective reactions like tearing, airway resistance and coughing. In our work [3], a previously unknown mechanism of TRPA1 activation hidden to experimental approaches was revealed by MD calculations. Experimental methods can capture the atomic resolution structure of the protein in its active and inactive snapshot-like state. However, the dynamic changes leading from the inactive to the active state are so quick and are affecting such a small region, that they often remain hidden for experimental approaches. Our MD calculations revealing these subtle changes are important for the elucidation of the whole activation mechanism of TRPA1, which is a crucial step for the design of new drugs.

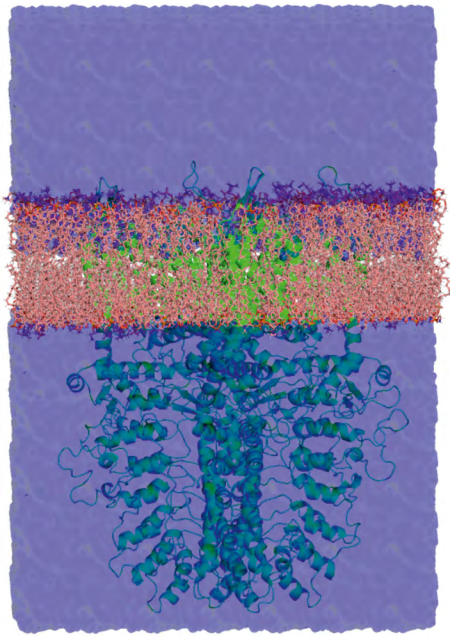


Figure 2: *The TRPA1 protein (green cartoon) embedded into membrane (red bar, the sticks represent the membrane bilayer forming phospholipids), with explicit water solvent on the extra- and intracellular side (blue transparent surface on the top and bottom).*

Also an important example of method applications is our project on somatostatin receptor complexes. Somatostatin is an (endogenous) peptide found in our body that regulates the production of several hormones (e.g. insulin, growth hormone) and is involved in cell division, immune response, stress and pain mechanisms. Among its receptors, SST4 has been proved to be responsible for the analgesic effects of somatostatin. In order to design an effective and selective analgesic, it is necessary to know the binding site, conformation and interaction pattern of somatostatin on SST4 at the atomic level, furthermore, how these parameters differ in the case of the other SST receptor subtypes. As a result of several years of work, we have successfully determined the binding mode of somatostatin and its known analogues to the SST4 receptor. In addition to the determination of the final binding position and pattern, the complete binding process of somatostatin to the SST4 receptor has been elucidated at the atomic level by molecular dynamics calculations [4], providing atomic structures of the intermediate receptor-ligand conformations that might be important in ligand binding (Figure 3).

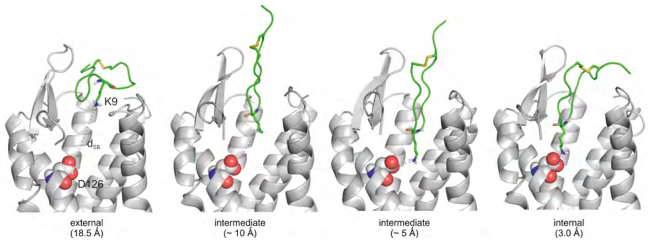


Figure 3: *Main steps of the binding mechanism of somatostatin (green cartoon, the central K9 amino acid highlighted with sticks) in external, intermediate (~10 Å and ~5 Å), and internal binding modes on SSTR4 (grey, cartoon). The numerical values are the distance (dSB) between the D126 amino acid (spheres) and K9, which decreases during binding. Source for the figure is Börzsei et al. Int. J. Mol. Sci. 2022, 23(13), 6878; https://doi.org/10.3390/ijms23136878. (For further permission to use this figure, please contact the Multidisciplinary Digital Publishing Institute.)*

[1] Zsidó et al., JCIM, 2021, 61, 4011
[2] Zsidó et al., Curr. Opin. Struct. Biol., 2021, 67, 1
[3] (Zsidó et al., Pharmaceuticals, 2021, 14, 988)
[4] (Börzsei et al. IJMS, 2022, 23, 6878)

Simulating the effect of micro- and nanoplastics on the environment and human health

Prof. Dr. Oldamur Hollóczki

Prof. Dr. Oldamur Hollóczki received his diploma in 2006 in chemical engineering at the Budapest University of Technology and Economics, and also his PhD in chemistry in 2011. Prof. Hollóczki was awarded the Alexander von Humboldt Postdoctoral Fellowship in 2012, which financed his stay at the Leipzig University (2012-2013), and the University of Bonn (2013-2014). He led a junior research group in Bonn, where he finished his habilitation in 2021. Since 2021 he works at the University of Debrecen, where he was promoted to full professor in 2022.

In recent years, significant attention has been drawn to the alarming environmental and health risks posed by the fragmentation of plastic waste into microscopic particles known as micro- and nanoplastics. These materials have been detected in unexpected areas of our planet, such as high mountain ranges or Antarctica, where the presence of plastic waste would be least expected. Considering the widespread distribution of micro- and nanoplastics, it is not surprising that they are also present in our foods and beverages, hence we are introducing them into our bodies at a rate of approximately the size of a credit card per week. Shockingly, a Dutch research group published even more alarming results last year: microplastics can be detected in the bloodstream [1].

Although we know that these substances do not belong in our bodies, information regarding their biological effects remains sparse. The challenge lies in experimental difficulties, which our research group aims to overcome by employing the toolbox of theoretical chemistry. We aim at providing detailed information on the interactions between micro- and nanoplastic particles and biomolecules, which may significantly aid in identifying potential points within highly complex biological systems that are sensitive to these pollutants.

Our previous studies have shown that the interaction of nanoplastics with proteins significantly depends on the material properties of the plastics [2] [3]. We examined changes in the secondary structure of a 12-alanine peptide in water and on different plastic surfaces using molecular modeling and quantum chemical methods. On the surface of a polyethylene particle, the peptide's α-helix structure stabilized, while on a nylon-6,6 nanoplastic surface, a conformation similar to β-sheet was observed. Such changes in the secondary structure of proteins can fundamentally alter their function, potentially leading to significant physiological consequences. Molecular alterations of this nature have been associated with various neurodegenerative diseases, such as prion diseases, Alzheimer's, and Parkinson's. Currently, the link between micro- and nanoplastics and these health issues remains unproven, but these similarities strongly suggest the need for further investigation into the impact of micro- and nanoplastics on the human body, especially the nervous system.

At the outset of our project registered at KIFÜ, it was clear that understanding the possibility and method of these particles entering the brain would be crucial for fully comprehending their effects. The transfer of compounds found in the blood to the brain is regulated by the blood-brain barrier (BBB), safeguarding our central nervous system from various toxins. The penetration through the BBB is also a critical consideration in the design of drugs that affect the brain, and numerous experimental and computational methods are available to study this process in depth. One such method involves transferring the studied molecule from an aqueous environment into a bilayer of DPPC lipids and quantifying the energetics of this process. For our calculations, we generated a model of approximately 5 nm diameter polystyrene nanoplastic particles [4]. The migration of the bare particle into the DPPC lipid bilayer occurs with a significant energy gain, suggesting that this nanoplastic would not pass through the BBB but remain within the hydrophobic core of the lipid bilayer. Typically, on the surface of nanoscale particles, a layer of one or more molecules, called a corona, forms in the body, fundamentally altering their surface properties and interaction with biomolecules. To account for this, we created three different compositions of biomolecular coronae on the plastic surface, involving cholesterol and protein molecules. Interestingly, the cholesterol corona facilitated the plastic's dissolution into the lipid, while the protein corona significantly hindered

it. In the presence of the protein corona, dissolution did not result in energy release but instead showed a substantial energy demand, indicating that in this scenario, the plastic cannot pass through the BBB. Nonetheless, these results unequivocally demonstrate that the corona fundamentally determines penetration through the BBB. Given the wide range of energetics for the interactions with the BBB, it is reasonable to assume that a corona could form, which enables the transfer through the BBB. Therefore, among the multitude of particles entering the body and reaching the bloodstream, some are expected to develop a corona on their surface that allows them to pass through the BBB [4].

Building upon our computational findings, our collaborating partners at the Medical University of Vienna conducted experiments on mice to determine whether micro- and nanoplastic particles indeed pass through the BBB. To facilitate the detection of these particles, they were labeled with a fluorescent marker when ingested with nutrients. The experiments not only confirmed the presence of particles penetrating brain tissue, in line with our calculations, but surprisingly revealed that this occurred extremely rapidly, within two hours of entering the gastrointestinal tract [4].

In light of these results, the most critical open question is whether particles that have reached brain tissue or other organs can be correlated with any abnormalities and resulting diseases. Thus, we plan to expand our computational simulations on the computing system of KIFÜ, investigating the interactions between relevant proteins in neurodegenerative diseases and plastic particles. With the collaboration of our partners, we aim to experimentally verify these computations to the best of our abilities.

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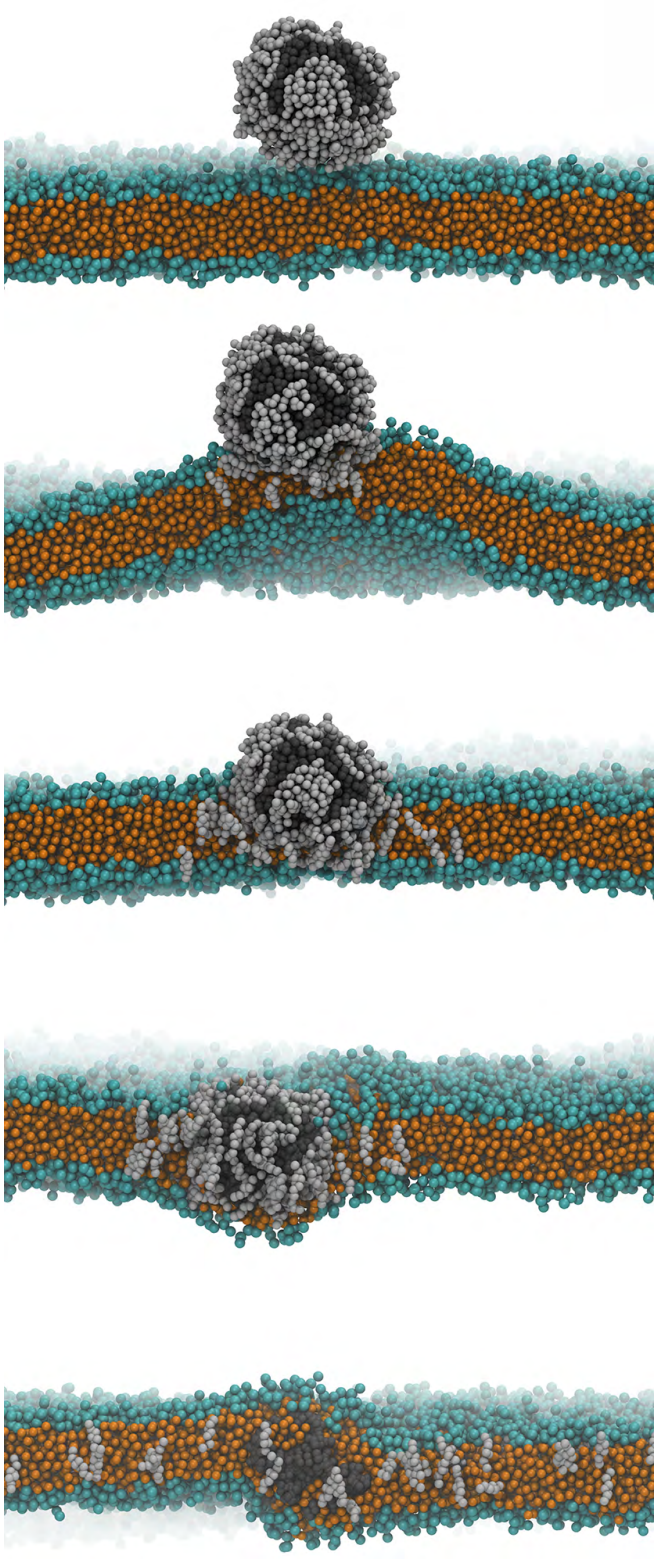

Figure 1: *The mechanism of sorption of a nanoplastic (black) model with a lipid corona (grey) into a DOPC double layer (green and orange), used as a model for the blood-brain barrier. In the first step, the particle approaches the membrane (above), which forms a bulge to enhance the lipid-lipid interplay. The nanoparticle then penetrates this bulge, followed by the desprtion of the lipid molecules into the membrane, while the lipid bilayer recovers its planarity.*

Continuous plasma dynamics on a discretized spatial grid

Zsolt Lécz, Szilárd Majorosi

Zsolt Lécz did his PhD studies between 2010 and 2013 at the GSI Research center in Darmstadt, Germany. During this period, he learned the basics of laser-matter interaction and its theoretical modeling. He received the PhD degree at the end of 2013, then next year he joined the Plasma Physics research team at ELI-ALPS, in Hungary. Over the years the theory of laser-plasma interaction has became his are of expertise and he actively investigated various cases, mainly concentrating on particle acceleration and short-wavelength radiation emission in laser-driven plasma. For these studies he uses particle-based kinetic plasma simulation codes, called particle-in-cell (PIC) codes, which are powerful and highly reliable tools developed for the investigation of such nonlinear interactions. These simulations can be run efficiently on high performance computers, such as the Komondor.

Szilárd Majorosi, started his career at the University of Szeged, in the department of Theoretical Physics, as a research fellow and lecturer between 2016 and 2021. His major research area was the theoretical investigation of laser field interaction with atoms, based on quantum-mechanical calculations. Since 2021 he works in the Laser-driven Particle Acceleration group at ELI-ALPS. His main task is the development of computer codes that can be used for numerical modeling of laser propagation in low density plasma. He plans to use the Komondor HPC to simulate and investigate advanced electron acceleration mechanisms, using his own code.

During my decade-long theoretical research, I have been investigating the interaction of high intensity laser pulses with matter using analytical and numerical models, where the matter is considered to be highly ionized (plasma state), and the laser pulse field is described as a strongly focused electromagnetic wave. In leading laboratories all around the world (also at ELI ALPS) the intensity of the lasers is so high that upon irradiation all kinds of matter become ionized and the released electrons acquire extremely high kinetic energy in a fraction of a single laser cycle. These "hot" electrons generate a strong electric field, by charge separation, leading to the acceleration of other electrons (or even ions) in a controlled manner in a well-defined direction. Thus, with the help of high-power lasers, particle acceleration becomes possible within distances of a few centimeters, which are nearly million times shorter than the distance required in conventional accelerator devices. This is the main driving force and motivation behind the research of laser-plasma accelerators.

Modeling the microscopic processes (on the scale of the laser wavelength: 1 micrometer) in three dimensions is a great challenge even for today's high performance computers (HPC). To obtain a realistic picture about the evolution of the electromagnetic field in the focal volume of the laser pulse, we need to calculate the trajectories of electrons and ions with close to attosecond temporal resolution, meaning that the time-step of numerical modeling is one billionth of a billionth of a second. This extremely high temporal resolution requires similarly high spatial resolution, which leads us to the nanometer-scale grid spacing. The quasi-point-like, charged particles move between these closely placed grid points in a way that their charge distribution modifies the electromagnetic fields surrounding them. Such highly nonlinear interaction can be modeled by solving the coupled Maxwell and relativistic Newton equations in a discretized space, paying special attention to the conservation and continuity laws that characterize the system.

As the focused laser pulse is really tiny (the radius of the focal spot is in the order of 10 microns), only a small spatial volume has to be simulated. However, the number of grid points is still very high, in the order of 109, and the fields, as well as the particles' motion must be calculated over thousands, or even hundreds of thousands, of iterations (time-steps). Based on this, a full simulation contains 1017–1018 CPU operations. This is a huge number, but assuming that 100 processor cores work at maximum efficiency, such simulation is accomplished within 10 days. However, researchers would usually need a shorter time period to simulate a given problem, especially if the effect of variable laser parameters has to be investigated. With the help of

really large computers (such as the Komondor in Debrecen) one simulation of this kind can be completed in one day if thousands of processor cores are used.

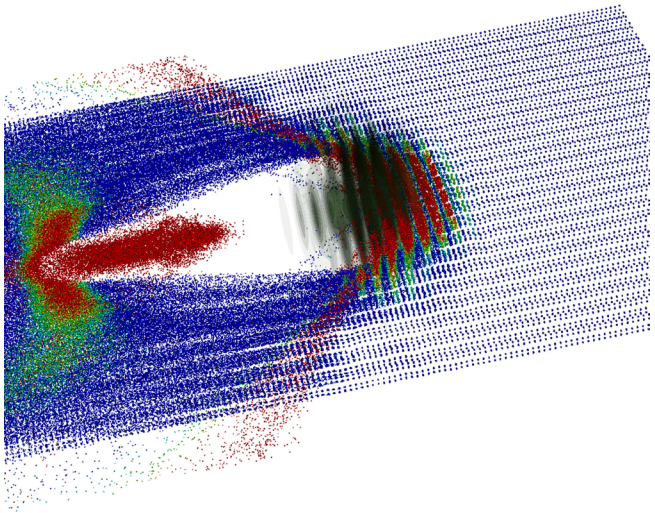

Figure 1: *Distribution of plasma electrons in a plane where the propagation axis of the laser pulse is found.*

In the picture above the cross-section of the plasma is shown in a plane that includes the propagation axis of the laser pulse. The colored points represent the electrons with a color scale (blue-green-red) following their increasing energy value, where the red color corresponds to the highest energy. In this picture we see the action of the Lorentz force on the plasma electrons, pushing them forward and in lateral directions, leaving behind a positively charged region, called ion cavity or wakefield. The ions are much heavier than the electrons, therefore they practically do not move as the laser pulse passes by at nearly the speed of light. This positive space-charge attracts the electrons and pulls some of them into the cavity, as it is seen in the figure at the end of this electron-free region. The wakefield generated behind the laser pulse is very similar to the pressure modulation that is experienced on the highway behind a larger truck. The propagation of the laser pulse and the "response" of the plasma is a very complicated process that can be accurately modeled only with the numerical method presented above.

One simulation domain is divided into several subdomains, and in each subdomain one or several processor cores calculate the field evolution and the motion of particles located in that region of space. Modern supercomputers have many processor cores, which work parallel (simultaneously) on the distributed tasks assigned to the subdomains. Each processor core can access a given portion of the computer's memory (RAM), where the particle and field data are stored. After one iteration is finished and each core has completed its job in its own domain, the particles can cross the boundaries between the subdomains, therefore their data will be transferred to another portion of the RAM. This data exchange, and communication between cores in separate processors, is the strongest bottleneck in parallel computing, as it decreases the overall simulation speed. In the last two decades, different hardware configurations and software strategies have been developed to reduce communication between processors, and these solutions are successfully applied in large supercomputers, as in the case of Komondor.

Currently, our research group is investigating a special case of laser-driven electron acceleration, where two pulses propagate in a gaseous plasma. The delay (or temporal distance) between the two pulses is very important, but the relative spot sizes and intensities are also equally important in the wakefield generation process. These parameters influence the shape and amplitude of the plasma fields, therefore performing an extensive parameter-scan is crucial to better understand the plasma dynamics and related electron acceleration. The supercomputers at KIFÜ provide great support for such complicated modeling, since beside the large amount of CPU cores many graphics units (GPU) are installed, which further accelerates the calculations. In the near future, we will publish a scientific article, the first one containing data produced with the Komondor HPC.

Simulation of attosecond processes

Dr. Balázs Major,
Dr. Katalin Geretovszkyné Varjú

Katalin Varjú is the Science Director of ELI ALPS and associate professor at the Department of Optics and Quantum Electronics, University of Szeged. In 2022 she was awarded the Physics Prize by the Section of Physical Sciences of the Hungarian Academy of Sciences for her achievements in attosecond physics.

Balázs Major is sensior research fellow, group leader at ELI ALPS, and also teaches as an assistant professor at the Department of Optics and Quantum Electronics, University of Szeged. In 2021 the editorial board of Journal of Physics B (IOP) selected him as one of the „emerging leaders" of his research field, and from 2022 he is the elected chair of Optica's Technical Group focused on attoscond sciences and high-field physics.

Since the beginning of the 21st century, attosecond physics has made meteoric progress. As its name suggests, researchers of the field study physical processes that take place in a billionth of a billionth of a second (i.e. in a few attoseconds, or 10-18 seconds). Two Hungarian scientists, Győző Farkas and Csaba Tóth, made an important contribution to the birth of this discipline in the early 1990s, and attoscience has been actively studied by members of the Hungarian research community ever since. This was one of the reasons why ELI Laser Research Institute was built in Szeged, which, as its name suggests (ELI ALPS – Extreme Light Infrastructure Attosecond Light Pulse Source), aims to become a unique scientific centre in this field.

The most important tool in this branch of science is a flash of light with a duration of a quintillionth of a second, the , light pulse', which can be used as a flashlight to capture objects moving at extremely high speeds. What can move so fast? Electrons in atoms, for example. How can we produce these flashes of light? Indirectly, also with electrons. In the late 1980s, French and American researchers succeeded in demonstrating a process known as high harmonic generation. In this process, short and intense laser pulses (such as the ones available at ELI ALPS) are used to illuminate noble gas atoms, tearing from them electrons, which then return to the atomic nucleus in the laser field and emit extreme ultraviolet (or even X-ray) radiation. This is where the contributions of Győző Farkas and Csaba Tóth were significant, as they showed that this radiation can take the form of attosecond flashes of light.

So the generation of attosecond pulses is based on the interaction of atoms and light (laser pulses). However, to produce a sufficiently bright flash, a light source suitable for experiments, for „taking pictures", a large number of atoms and laser light need to interact (see foreground of Figure 1). Since such an experiment involves billions of millions of atoms, the simulations needed to better understand the process can only be carried out using computers with high computing power. To this end, we have been using the capacities of high power computers (HPCs) provided by the Governmental Information-Technology Development Agency (KIFÜ) in Szeged and Debrecen for several years. With a self-developed software, and in collaboration with Romanian researchers, we can model the process of high harmonic generation not only at the level of a single atom, but also at the level of many atoms. This provides us with a unique simulation environment that has helped us optimize such light sources, or explain experimental observations and the underlying processes.

A notable product of our collaborations last year was a series of experiments with researchers in Berlin, where extreme ultraviolet light beams optimized with our help were split into two and then focused onto noble gas atoms (see the background in Figure 1). By varying the overlap between two light beams, and by making the constituting attosecond pulses reach the atoms simultaneously or at different times, we were able to map the atomic process in which an electron is torn out of an argon atom under illumination. The photo of the captured moment made the cover page of Optica, a leading journal in the field (see Figure 2). These results pave the way for the future use of attosecond pulses not only in observing but also in controlling these processes.

Another great achievement of the previous year was the development of an attosecond beamline at ELI ALPS Research Institute in Szeged. In this case, too, we used

the HPC capabilities of KIFÜ to analyze the potential problems associated with a special generation concept (using a so-called annular laser beam) and to determine the laser and gas medium parameters (e.g. gas pressure) that would lead to successful experiments. Thanks to these calculations, we could contribute to the generation of an XUV source with exceptionally high flux, providing a unique tool for researchers who aim to study the fast processes mentioned above. This result was published in the journal Ultrafast Science, once again highlighted on the front cover (see Figure 3).

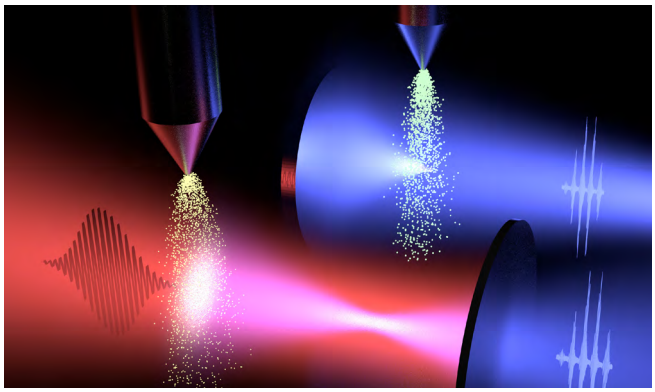

Figure 1: *In the foreground, an artistic representation of the high harmonic generation process: a short (a femtosecond, or 10^{-15} seconds long) laser pulse (red beam and its waveform) is focused onto a cluster of atoms (yellow balls flowing from a metallic tube), and the light-matter interaction results in a short wavelength of extreme ultraviolet radiation (blue beam). A filter is used to separate the laser light from the attosecond pulses (purple waveform) for subsequent applications. Background: the generated pulses are focused into a different gas jet using a mirror during the experiments.*

Figure 2: *When an argon atom is illuminated with two attosecond pulse trains (purple waveforms), it absorbs four photons (white balls with tails) and then emit three electrons (yellow balls with tails). By varying the spatial and temporal overlap of the attosecond pulses, the physical process that leads to the electron exit can be mapped. The figure has been chosen for the cover page of Issue 6 of Optica in 2022: https://opg.optica.org/optica/aboutthecover.cfm?volume=9&issue=6.*

Figure 3: *The cover page of Issue 1 of Ultrafast Science in 2022, featuring the 3D graphic representation of the operating principle of one of the beamlines at ELI ALPS.*

Transition metal catalysis: from biomolecules to catalysts

Transition metals, such as iron or copper have been playing a key role in the functioning of living organisms since the appearance of life on Earth. Among others, iron-containing enzymes are responsible in our body for the transport of oxygen, breathing and metabolism of drugs. Other transition metals, such as ruthenium, palladium or platina are used as catalysts in industry for chemical conversions in order to produce products faster, more cheaply, and more efficiently. Societal challenges motivate us to create better drugs with less side effects to treat diseases. Similarly, sustainable development and the protection of our surroundings requests industry while maintaining the level of industrial production to replace rare, toxic and expensive transition metals (such as palladium an platina) with earth-abundant, environment-friendly transition metals such as iron and copper.

However, in order to reach these aims, many obstacles have to be overcome. The design of both new drugs and new catalysts requires time, research and work power, and in all cases lasts for years. A key component of this process is whether we can understand the mode of action of drugs, or how catalysts facilitate chemical reactions. Modelling tools play a key role in this. Using computers and theoretical models we can reveal the structure, properties and reactivity of small and large molecules, including biopolymers. Afterwards, we can use the obtained results to establish predictive models for the design of a new generation of drugs or catalysts.

Transitions metals, especially iron, play a central role in our research. One of our main interests is the investigation of iron-containing enzymes, with special focus on the metabolism of drugs1 and on signal transduction in living organisms.2–4 A typical protein structure is shown in Fig. 1. We have investigated the mode of action of nitric oxide in the human body and in bacteria. Although nitric oxide is most frequently mentioned in the context of smog (as one of its main causes), still nitric oxide produced endogenously in the body plays a key role in the cardiovascular, nervous and immune systems. The only known receptor of nitric oxide in man is soluble guanylyl cyclase (sGC) whose malfunctioning leads

Members of the research group: Julianna Oláh, Zsolt Benedek, Marcell Papp, Ahmed M. Rozza, Joseph Kfoury

On the research group

Julianna Oláh is an associate professor in the of Department of Inorganic and Analytical Chemistry, at BME, she obtained the title of Doctor of Sciences in 2023. Her research focuses on the computational investigation of the structure and reactivity of enzymes and transition metal compounds.

Zsolt Benedek studied the mechanism of biomimetic nitrogen fixation using computational methods during his Ph.D. and obtained the degree at the George Olah Doctoral School at BME in 2021. He is currently a research fellow in the Institute of Physics and Astronomy at ELTE University. where he investigates the electronic properties of solid-state quantum bit candidates and develops strategies for quantum bit design.

Joseph Kfoury obtained his MSc degree in chemical engineering at the University of Balamand in El-Koura, Lebanon. He won the Stipendium Hungaricum Fellowship of the Tempus Public Foundation, in the same year, and he uses quantum chemical calculations to investigate biomimetic nitrogen fixation and spin cross-over compounds.

Ahmed Mohamed Rozza obtained his M.Sc. degree in biotechnology in 2017 at the Al-Azhar University in Egypt. His doctoral studies were funded by the Stipendium Hungaricum Fellowship of the Tempus Pubic Foundation between 2018-2023. He currently works for the Research Centre for Natural Sciences, but maintains his working relationships with the group. His research interests include protein systems and biopolymer/water mixtures, and he applies molecular dynamics simulations and hybrid quantum mechanics/molecular mechanics calculations.

Marcell Papp studied biomimetic nitrogen fixation and the mechanism of H-NOX proteins at the Department of Inorganic and Analytical Chemistry, BME. He pursues his doctoral studies at ETH, Zurich and investigates amyloid aggregation, liquid-liquid phase equilibrium of biopolymer and its effect on protein aggregation.

to widespread and serious diseases in the society. Worldwide, intensive research is directed at the understanding of the functioning of sGC, in order to use the insights gained for the design of better drugs. In our works we studied how nitric oxide can get to the active site of the proteins, and how it exerts its effect, what kind of structures could be produced, what is the active form of the enzyme, whether one or two nitric oxide molecules contribute to the process and what is their binding place.

Our other major research field is biomimetic nitrogen fixation, which involves the binding of nitrogen present in air and its transformation to ammonia. Ammonia is one of our most important industrial raw materials; more than 150 million tons are produced each year using the Haber-Bosch process that is responsible for 1% of global energy consumption and 3% of greenhouse gas emission. However, there are bacteria which are capable of turning air nitrogen into ammonia at room temperature in a much more efficient and economical way. The concept of biomimetic catalysis refers to mimicking the functioning of naturally occurring enzymes (see Fig. 2.). Such catalysts were developed for nitrogen fixation by an American research group,5 and we have studied their functioning using computational tools: with quantum chemical calculations and microkinetic models.6-9 First, we determined which compounds could be formed in the catalytic cycle, and what is their relative energy and structure. Then we investigated the potentially ruinous side reactions that may decrease the efficiency of the catalysts or which may even destroy it. Finally, we suggested a model to explain the functioning of the overall catalytic system and pave the way for the design of better catalysts.

Research is a continuous challenge that requires constant attention, effort and resources. We are indebted to the supercomputing facilities established and maintained by KIFÜ, without them we could not have achieved our results.

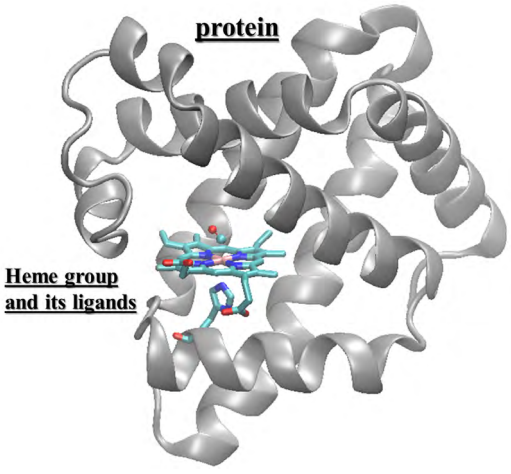

Figure 1: *A typical heme containing protein. The main chain of the protein backbone is shown in grey while the iron-containing heme group and its ligands are coloured.*

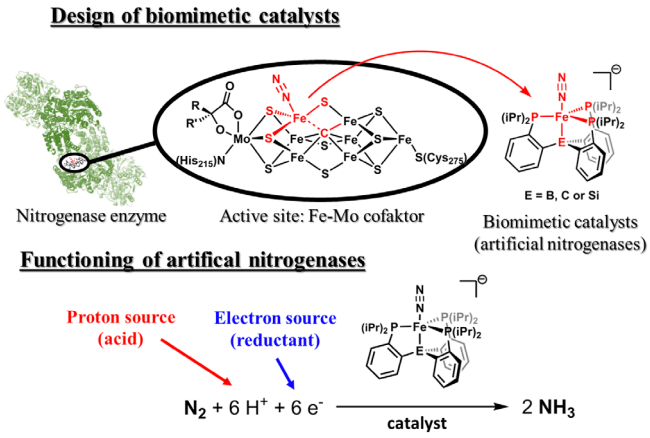

Figure 2: *Fundamentals of biomimetic catalyst design for ammonia fixation: Mimicking the structure and reactivity of the naturally occurring nitrogenase enzyme we would like to create better catalysts*

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Generation of gap junctions from connexin hemichannels

Connexins (Cx) are membrane embedded hemichannels that reside in two adjoining cell membranes. One hemichannel from one cell membrane and the other from the opposite cell membrane couples to form gap junctions (GJ).

Our group has shown [3] that astrocytes. – a group of cells in the central nervous system -, not only provide a supporting role -, but they are able to act synchronously, and their synchronization even preceedes the synchronization of neurones. This cooperation of astrocytes may be responsible for the learning phase during physiological slow wave sleep or during a pathological condition, named absence epilepsy. We supposed. that coordination of astrocytes may be realized through gap junctions, because a direct cell-cell connection seems most suitable for synchronization.

To identify this mechanism, specific blockers are needed, that inhibit Cx43 gap junctions, the type that is abundant on the surface of astrocytes. Unfortunately, there is no specific inhibitor for the Cx43 type GJ channel, furthermore, there is no really specific inhibitor for GJ channels, in general.

Our goal, therefore is to develop a specific molecule, that inhibits gap junctions, most importantly the type Cx43. To achieve this goal, we need to understand cell-cell coupling at the molecular level. Recently, the structure of several Cx subtypes have been determined by X-ray diffraction or cryo-electron microscopy. Starting from the first X-ray structure of Cx26 we modelled the Cx43 hemichannel [5] and showed that commonly used inhibitors do not even dock to the previously thought extracellular region of the connexins. Thanks to the KIFU HPC infrastructure we could not only map the raw hemichannel model, but we could follow the hemichannel structure after 50-200ns of molecular dynamics run performed by the Desmond program package. Next, we modelled the whole Cx43 GJ protein and identified central regions, named stabilization centers (SCs) [1] that hold together the whole structure, such as hubs in a network. Using molecular dynamics calculations we have shown, that conserved 55N, 56T and even residue 57Q, which is characteristic for Cx43 remain in stabilization centers even after 100ns [6]. Since lipid-protein interactions are important in gap junction dynamics, we have used an all atom model, that is all protein atoms, membrane lipid atoms and water atoms of the environment were included explicitly. The system size rose over 300 000 atoms, which could not be handled by a regular workstation, so molecular dynamics could only be performed using HPC KIFU Debrecen2 machine, that offered GPU usage. This GPU could accelerate our calculations so much, that we could achieve a speed of 6ns/day.

The structural understanding of Cx channels advanced greatly, when cryo-EM structure of Cx31.3 hemichannel became available [4]. This subtype is unable to form GJs, rather remains in hemichannel form in nature, therefore it seemed to be a good template for modeling hemichannel structure of Cx43. Starting from this 3D structure we positioned two Cx43 hemichannel models to 5Å distance, and approached them gradually to achieve their physiological distance in a GJ (Fig. 1). We have performed 100ns molecular dynamics calculation at each stage and followed the step-by-step generation of stabilization centers.

Functional Pharmacology Research Group

The research was lead by László Héja at the Functional Pharmacology Research Group of the Institute of Organic Chemistry at the Research Centre for Natural Sciences.

The main research projects of our group is related to both chemistry and biology: Exploring the role of astrocytes in modulating neuronal function in healthy and diseased brain. identifiing potentially druggable (primarily astrocytic) target proteins or mechanisms in pathophysiological conditions

The applied multidisciplinary approaches include in vitro and in vivo simultaneous fluorescent imaging electrophysiology, toxicology, synthetic chemistry, in addition to in silico modelling, described.

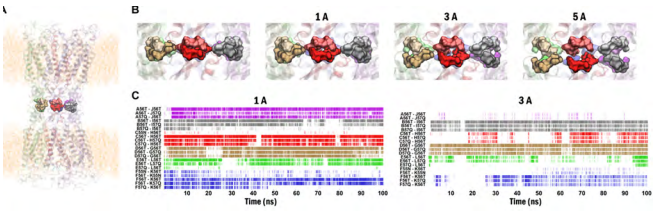

Figure 1: *Increasing hemichannel distance reduces the number of stabilization centers. A, The model of Cx43 GJ channel. B, Stabilization centers are weakening during molecular dynamics simulation as HCs move off each other. C, Decreasing number of stabilization centers.*

Next, we posed the question of how these residues are positioned so precisely, that they are in ideal distance to create H-bonds with each other. It is known, that a number of Cys residues are located near the gap region, and these Cys residues may open up depending on the redox environment [2]. We speculated, that these Cys residues may have a role in generating the full GJ structure. Disulfide bonds were opened up in the hemichannel models and we performed molecular dynamics simulation using both the „open" and the „closed" disulfide version of the double HC model. We found that opening/closing of the disulfides are indeed related to the coupling of the hemichannels (Fig.2) [7].

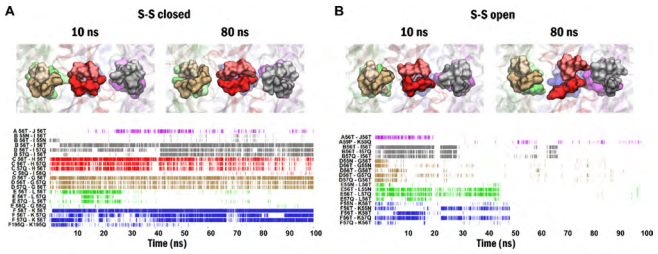

Figure 2: *Disulfide bond opening disturbs the inter-hemichannel stabilization center system and rearranges H-bonds. Stabilization centers at open (A) and closed (B) disulfides.*

Based on our results, targeting the disulfide-rich region opens up the possibility for developing selective connexin inhibitors. Furthermore, inhibiting unique stabilization center elements, specific for Cx43 may allow the development of Cx43-specific inhibitors in the future.

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The interpretation of reactions and calculation of spectroscopic properties


András Stirling, Péter Pál Fehér

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Péter Pál Fehér is a chemist who obtained his PhD in 2019 at the University of Debrecen where he studied reaction mechanisms of transition metal catalyzed processes with computational chemistry using the HPC infrastructure provided by KIFÜ (previously NIIFI). He currently works as a research fellow in the Theoretical Chemistry Research Group at HUN-REN RCNS where besides reaction mechanism studies he performs molecular dynamics simulations and works on method development in photochemistry.

The fundamental motivation of our project is to understand chemical phenomena at atomic and molecular levels. In each of our works we first establish a molecular model that has a size suitable to describe the given chemical property or the reaction mechanism with the desired accuracy. The molecular model (the system under investigation) is essentially a collection of atoms (nuclei and electrons) described by 3D coordinates. After the model is established, we determine the energy of the whole system and the forces acting between the individual atoms. In most cases the calculations involve the approximate solution of equations formulated within the framework of quantum mechanics (such methods are called quantum chemistry). This is where the computational resources of KIFÜ are utilized: we run software that solve highly demanding equations by utilizing the HPC infrastructure. The largest factor contributing to the cost of the calculations is evidently the size of the model but we can also include ancillary conditions like solvent effect, electronic or magnetic fields, etc. or we can model the time evolution of our system (molecular dynamics) by performing a series of calculations. Therefore, compared to traditional desktop computers, HPCs allow us to extend the chemical models or to perform a manifold of calculations in parallel. Computational modeling and simulation based on electronic structure are highly useful for us in two areas: the prediction of spectroscopic properties and the exploration of reaction mechanisms. In the following we showcase thematically grouped studies that we have worked on in recent years. We focus on the chemical impact and the role of the calculation without going into technical detail.

Exploration of reaction mechanisms: Even with the constantly developing toolset available in experimental chemistry, the speed at which chemical reactions take place coupled with other synthetic difficulties often do not allow us to obtain enough information about the individual steps that link the reactants and products in a reaction. Computations, however, do not suffer from these limitations and they can be used to explain how or why a rection does or does not yield a particular product. In one of our studies, we have worked together with an experimental group from Italy to investigate the mechanism of a reaction that leads to a complex polyheterocyclic product. Fig. 1 shows the reaction outline together with an energy profile of the final segment of the calculated reaction pathway.

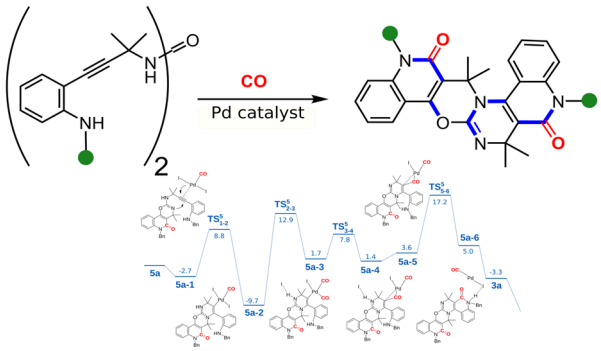

Figure 1: *The cascade reaction leading to the product with fused six-membered rings together with the energy profile of the terminal segment of the reaction mechanism. The 8 bonds shown in blue are formed during the reaction.*

The novelty of this reaction is that in contrast to previously established processes the main product has not five-, but six-membered rings fused together. This result could not be explained using experiments, so our task was to establish a computational model that complements the experimental observations. We have explored several elementary steps and determined which of those steps are consistent with the experiments. We have found that the number of atoms in the rings are determined already in the earliest stage of the reaction where the catalyst binds to the triple bond of the substrate. Due to electrostatic reasons, this step can only lead to a six-membered ring and this first ring predisposes all the subsequently formed rings to be six-membered as well. The understanding of this cascade reaction is expected to contribute to the targeted synthesis of similarly complex, fused ring compounds [1].

The use of frustrated Lewis acid-base pairs as hydrogenation catalysts has been at the forefront of synthetic chemistry in the recent years. This motivated us to investigate the hydrogen binding affinities of such Lewis pairs. We have employed molecular dynamics simulations in which the energies and forces were provided by quantum chemical calculations. We have described the mechanism of the binding process and discovered an asymmetry in the energy distribution of the dissociated hydrogen atoms that may have a key influence on the subsequent part of the mechanism [2].

The Suzuki-Miyaura coupling is a remarkably successful strategy for the creation of C–C bonds. American researchers have designed a new variation of this reaction that involves easily accessible Ni-phosphine complexes instead of traditional noble metal (Pd, Rh) complexes as catalysts. We have performed calculations based on their experimental results to describe the catalytically active species. This work has led to insights not directly available from experiments. We have demonstrated how the size of the phosphine ligands influence the reaction mechanism: a catalyst with smaller phosphines can rearrange more easily which in turn simplifies the reaction mechanism (Fig. 2). We have considered significantly different reaction conditions (catalytic and stoichiometric) and compared the two models to explain the relevant experimental observations [3]. With this work together with a previous one we have shown when and why it is necessary to go beyond static models and perform a more complete statistical exploration like free energy simulations to gain a deeper understanding about certain types of reactions [4].

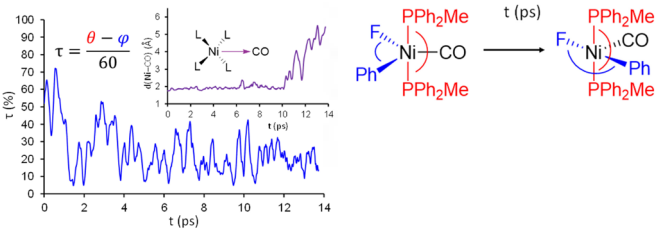

Figure 2: *Time evolution of the rearrangement (fluxionality) between trigonal-bipyramidal (τ ≈ 100%) and square-pyramidal (τ ≈ 0%) isomers of a Ni-phosphine complex. The inset shows the evolution of the Ni–CO distance and the dissociation event at 10 ps.*

Method development studies: In the more recent years our group has been focusing on photocatalysis, or more generally on the reactivity of excited states. We have published a paper where we introduced a new protocol for the simulation of UV-vis spectra [5]. Our method considers temperature, solvent and nuclear quantum effects. As most of these effects are only approximated or entirely neglected in traditional approaches, we demonstrate how their inclusion affects the simulated spectra (Fig. 3). In an extension of this work, we have combined quantum chemistry and machine learning to predict excited state redox potentials [6]

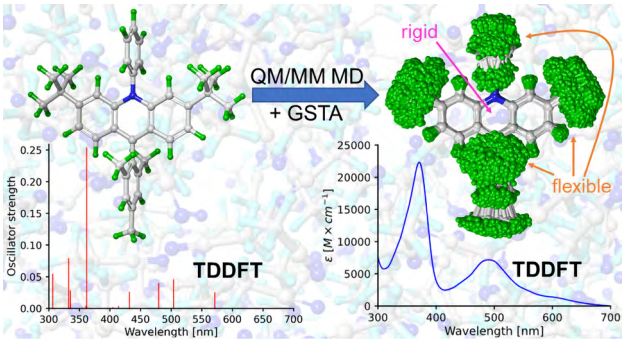

Figure 3: *The new protocol provides a more realistic spectrum compared to traditional approaches if we consider the effects of temperature, solvent and the quantum nature of the nuclei.*

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