HPC ECHO

From Science to Innovation

2021

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FOREWORD

Mr. Krisztián Kongó
Vice-president of KIFÜ

What a busy year we had! In 2021 we were focusing on preparing the scene for the further development of our HPC infrastructure. Our new supercomputer, Komondor arrives in the springtime of 2022 thus we can provide 5 petaflops of computing capacity for our users to support their research. The HPC team made these tasks a priority in the past year. It really takes a village!We are proud to publish the second issue of HPC Echo, which highlights research projects from different disciplines carried out in 2021. We do hope that with a larger capacity, we can expand the number of scientific fields that benefit from our infrastructure!

Mr. László Mohácsi
Head of HPC Competence Centre

The annual HPC Echo 2021 aims to present the outstanding research carried out in 2021, supported by the KIFÜ HPC Competence Centre. In this year's issue, we are delighted to report on 8 outstanding research projects. The fields of application are diverse, from studying microbial ecosystems and qubits to analyzing wine terroirs. Let's have a closer look at these research projects in the following pages!

AGRICULTURE   BIOLOGY   CHEMISTRY   PHYSICS

The investigation of the microbial terroir of Mád Wine Region

Research group members: Dr. Judit Remenyik, Dr. László Stündl, Dr. Attila Dobos, Dr. Melinda Paholcsek, László Csige, Dr. Zoltán Kállai, Dr. Nándor Rakonczás, Péter Dávid, Péter Zsombor Fauszt, Anna Anita Rácz, Dr. Gábor Fidler, Erzsébet Szőllősi

About the research group

The Center for Complex Systems and Microbiome Innovations (KRéMK) at the University of Debrecen develops (bio)monitoring services suitable for the complex study of environmental, farm animal and wildlife biomasses. Biomass composition is determined using state-of-the-art molecular analysis methods. For data analysis, specialized bioinformatics software are used. To cover the huge computation demand of these programs, the KIFÜ HPC cluster is used.

Thanks to the new-generation sequencing technologies (NGS) the importance of microorganisms in viticulture and oenology is obvious. Minerality is no longer identified with the bedrock, but with the soil and the fungal network and microbial community within it. The nutrition, growth, yield of the grapes, the management of environmental stress, the protection against diseases and pests, the control of weeds is all inconceivable without microbes. Metabolites produced by the billions of these microbes are the main contributors to the quality and fragrance of wine.

Figure 1. *The landscape of Mád with its surroundings of the Tokaj Wine Region in Hungary. The Borsay Castle of the Mád Wine Academy of the University of Debrecen. Furmint berries carry complex microbial communities on their surface contributing to the unique minerality of Tokaj-wine.*

The primary origin of the wine microbiota is vineyard soil, grapevine trunk and ultimately berry where several factors such as climate condition, topographical location, precipitation, and season could influence its diversity. The terroir is primarily defined by the fungal network and microbial community. An overwhelming body of evidence has demonstrated that wine terroir characteristics are related to regional microbial community compositions. Although, it is a big challenge for the research to clarify how do fungal networks and microbial communities in the soil amend terroir characteristics to evolve in the wine.

Researchers at the University of Debrecen in collaboration with Mád Wine Academy aim to explore the terroir of the world heritage Tokaj-Hegyalja (Tokaj-foothills)

Wine Region which is a historical wine region located in north-eastern Hungary (Figure 1). The slopes where the vineyards are planted create a favourable heat regime and microclimate for the wine grapes. High-throughput NGS sequencing techniques are used to analyse soil, grapevine trunk and berry samples to decipher the microbial terroir of Mád wine region evidencing three different agronomic managements. In collaboration with Pallag Experimental Station of Horticulture we examined the ability of seven different grape rootstocks to the microbiota of the grapevine trunk. It is also important to clarify how could one select and preserve the most appropriate microbial composition to preserve the authenticity of the terroir.

Biogeography was shown to have a prominent effect on the biological diversity that proved to be outstandingly good in Mád wine region (Figure 2A). The microbial footprints proved to be remarkably different in the case of soil
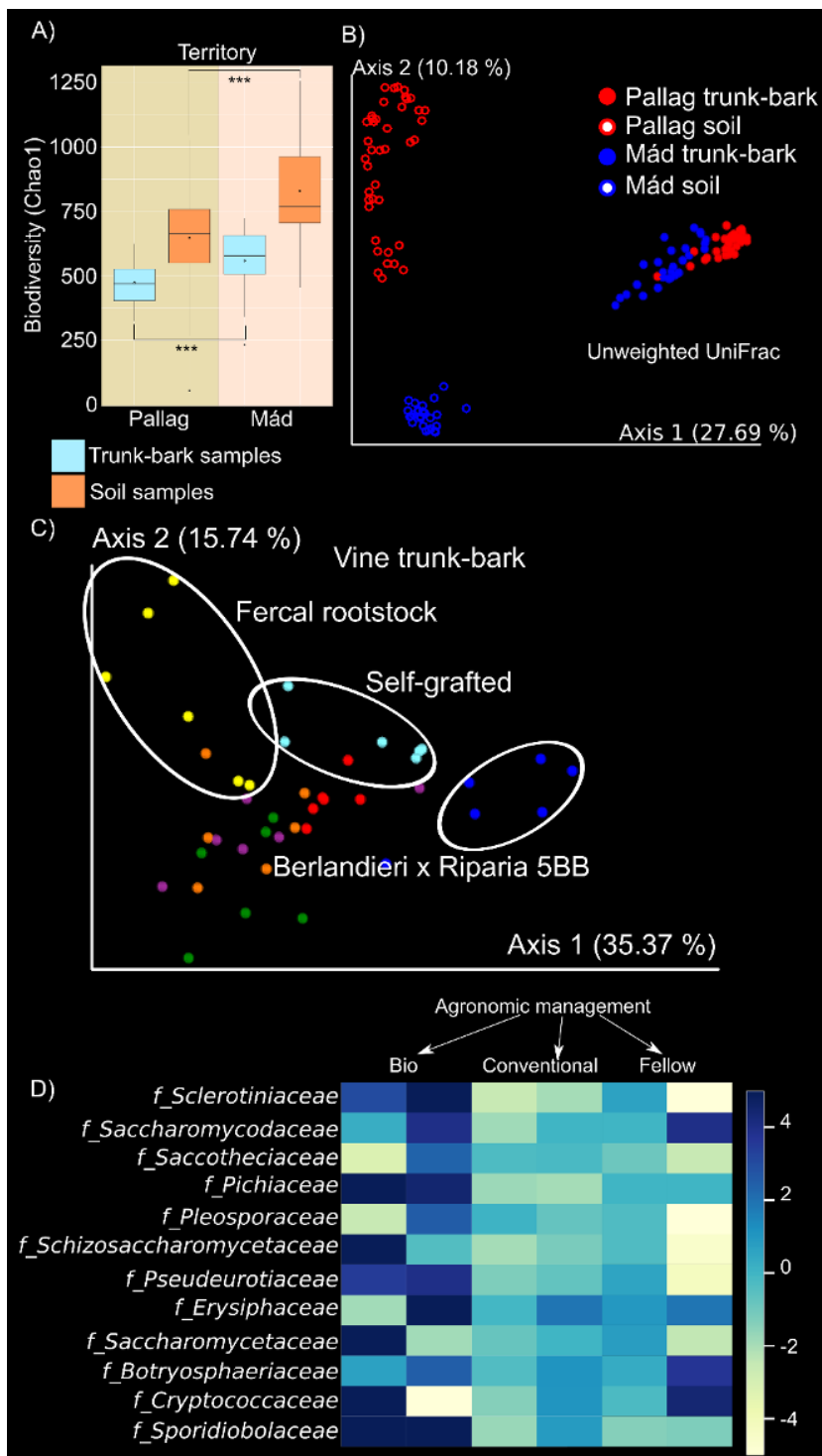
Figure 2. *Biological diversity of the soil and trunk-bark microbiota of the investigated viticulture regions of Mád and Pallag. (Figure 2A). Spots represent different communities correlating with the similarities and alterations in their taxonomical compositions (Figure 2B). The effect of the rootstock in the case of the seven different grape grafts from Pallag (Figure 2C). The differences in the relative occurrence of fungi due to different agronomic managements of Furmint berries are shown (Figure 2D).*

samples of the two different Hungarian vitivinicultural regions (Mád vs. Pallag), and surprisingly similar for grapevine trunk samples (Figure 2B). This might be explained by the same vine roots. Interestingly, the effect of the rootstock on the microbial community compositions was very pronounced in the case of the seven different grape grafts from Pallag. The microbiota; Fercal, Berlandieri X Ripari 5BB and the self-grafted vine trunk formed distinct areas in the two-dimensional PCoA plots (Figure 2C). Berries carry a wide variety of microbes from the grape environment, many of which are known for their role in the fermentation process of must. The alterations in complex microbial communities of the Furmint berries from three different cultivation areas were also determined. Samples were collected three times a year in 2020; July 7, August 31, October 05, where July month was used as the control time point. The most important fungi in winemaking are the yeasts which are shown (Figure 2D).

In complex microbial systems, there is a tooth with nails battle for evolutionary supremacy. Microbes need to constantly keep up with their competitors and prevent them from gaining any advantage. To illustrate this interracial arms race the Red Queen hypothesis is often used which is adapted from the classic Lewis Carroll work Through the Looking Glass. After Alice runs through the Garden of Live Flowers, the Red Queen tells her, „It takes all the running you can do, to keep in the same place". As there are no permanent community compositions, we described the equilibrium microbiomes of the vine soil and grape trunk samples (Figure 3A). A further important feature of the community dynamics is the butterfly effect, so even small changes in the initial states are going to be magnified exponentially. Network analyses are often used to study the structure and dynamics of real complex systems. We hypothesized, that the more connections a microbe has, the more influential its role for the whole community. The most strongly anchored microbes were considered as driver microbes, having greater adaptation. These microorganisms have a crucial role in building up the community safety net (Figure 3B). The ascades discovered in networks are microbial clusters characterized by the fact that their microbes form smaller, closed communities. Within these, members benefit from each other's existence, but at the same time share common resources under strict and superior conditions without being completely seized. By comparing community modularity data, we investigate which microbial interactions are significantly affected by comparing conventional and biodynamic agronomic managements.

We also decipher the antimicrobial resistance profiles of the wine yards (Figure 3C). As microbial communities are collective catalysts for biochemical processes in soil, they can also provide an insight into the transformation

and degradation of various organic matter and the elimination of chemicals, pesticides and toxins. Functional metagenomics was used to estimate metabolic processes provided by the core microbiota (Figure 3D).

Our major goal is to unravel compositional patterns between the grapevine trunk and berry microbiomes and the chemical composition of the wine to predict product quality and minerality using machine learning algorithms.

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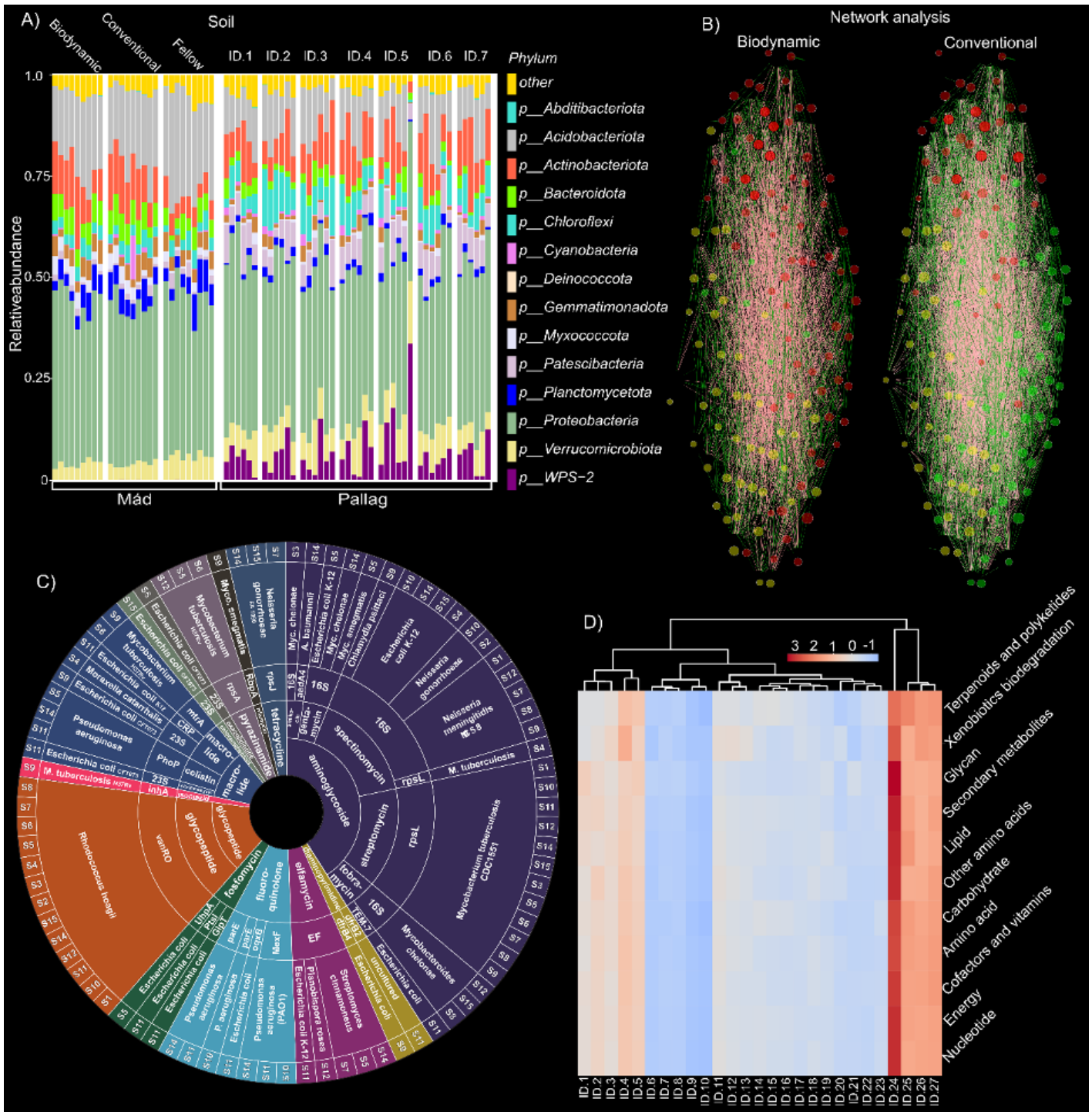

Figure 3. *Equilibrium microbiomes of the vine soil and grape trunk samples (Figure 3A). Network analyses for studying the structure and dynamics of the complex microbiota (Figure 3B). Antimicrobial resistance profiles of the wine yards (Figure 3C). Metabolic processes are provided by the core microbiota (Figure 3D).*

The dynamics of microbial cooperation with diffusible public goods

Gergely BOZA, István SCHEURING

Gergely Boza and István Scheuring are researchers at the Institute of Evolution, Centre for Ecological Research in Budapest. They both study problems related to theoretical ecology and evolutionary biology using mathematical tools and computational models. This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 952914.

Unicellular organisms, mostly bacteria and archaea, form a particular type of microbial ecosystems, often inhabiting surfaces, such as the skin or gastro-intestinal system of animals or humans, dead material, root surfaces, or any nutrient-rich (or limited) environments, etc. A great diversity of microbes form complex microbial communities, called microbiomes (Figure 1).

Figure 1: *A graphical representation of a microbial ecosystem. Different microbes live in close vicinity of each other held together by structures, called the biofilm matrix, produced cooperatively by the members.*

We are only beginning to understand the complexity and diversity of microbial ecosystems while there are many open questions about their structures and functioning.

The composition of a microbiome shows regularities: while particular species can be replaced with functionally similar ones, the major functional groups, or guilds, and certain types of interactions are generally present. For example, almost all microbial ecosystems are flooded with extracellular energy-rich products that can serve as a food source for ecosystem members, while these are often produced by only a very few species. This raises an interesting problem. The production of such energy-rich products is often costly, either because it is a loss of biomass for the producer, or because the enzyme that catalyses the production is very costly to synthesize. Biological capabilities are always in a trade-off, meaning for example that using energy/time/resource for one task drains energy/time/resource from another task(s). Hence, it is easy to show, that the time and effort spent on producing these freely available products decreases the efforts put in other, self-maintaining activities, such as growth, survival, or reproduction. Therefore, the producers can have a disadvantage compared to the non-producing consumers. Yet, such products still seem to be extremely common in microbial ecosystems. The question is: why?

The framework of evolutionary game theory has proved useful to understand and model such situations, the so-called social dilemmas. Producers are the co-operators, the ones whose costly cooperative actions benefit others beside themselves, while the non-producing consumers are the free-riders or cheaters, who do not pay any cost of cooperation but still can enjoy the benefit of it. And the diffusible materials are public goods that generate social conflicts between microbes. Since the production of this material is costly, without additional mechanisms, free-riders displace co-operators in the population.

Spatial population structure, in which individuals occupy a surface and have limited motility and dispersion, has been demonstrated to support cooperation. We were interested if such mechanisms can also explain the thriving of producers in microbial ecosystems. Therefore, we developed a spatially-explicit, individual-based model to study the competition dynamics between producers and free-riders (Figure 2).
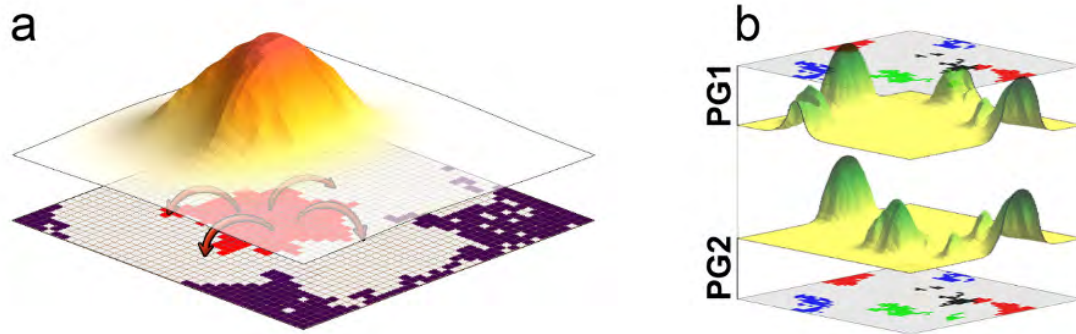

Figure 2: *A structure of the individual-based model. (a) The habitat, one point of a rectangular grid, can be occupied by one individual cell, be it a producer (bottom layer, red shading) or free-rider (bottom layer, black shading). The producer colony generates the diffusible material, the public good, that builds up a concentration profile (top layer) that decreases as moving away from the colony centre due to the diffusion, consumption, and degradation of the material. (b) A snapshot of a simulation. Generalists [1,1] (red) produce both type of public goods [PG1: 1=production/ 0=no production, PG2: 1=production/ 0=no production], specialists [1,0], [0,1] (green and blue) produce only one, and free-riders [0,0] (black) produce none. The actual concentration profiles are shown by the green-shaded layers.*

In the model, an individual occupies one specific location and interactions takes place with others in its surrounding. We model this as a cellular automaton consisting of a regular grid of cells, which serve as the location (or habitat) the microorganisms can occupy (Figure 2). Competition is local and success depends on the fitness, which correlates benefit of the public good taken up from the environment. Producers also pay a cost of production, which is deducted from the benefit. Once competitively superior individuals reproduce by cell division, the offspring can only occupy spaces in the close vicinity of the parent. The public goods produced by the producer types can, however, diffuse thus can affect others far away from the source. We model two public goods (PG1 and PG2), and hence we can have a generalist that produces both, specialists producing either, or free-rider producing nothing (Figure 2).

Our results demonstrate that at low diffusion rates (when the produced material does not diffuse far away from the colony) the generalist strategy wins (Figure 3, left-hand side), at high rates of diffusion, the free-rider wins and displaces the producer types. Once producers are gone, cells starve to death and the whole population collapses (Figure 3, right-hand side). At medium diffusion rates, the free-rider coexist with the producers, either with the generalist, or with one or two of the specialists, but the four types can never coexist for a long time (Figure 3, middle).

These findings highlight the importance of population structure in stabilizing microbial ecosystems, as well as demonstrate that the diffusion properties can greatly affect the outcome of competition between different microbial strategies and types. This also means that modifying the diffusion properties of the habitat the microbes occupy can shift the balance between the different types of producers and consumers of diffusible public goods.
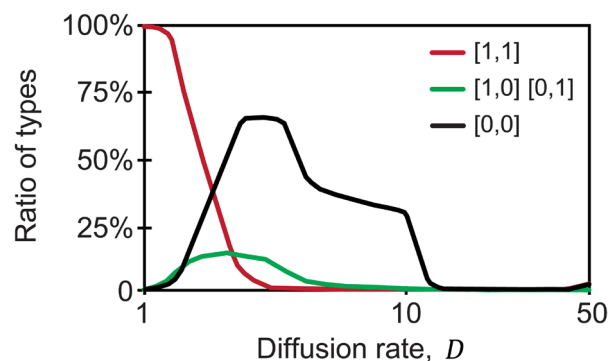

Figure 3: *Average results of numerical simulations.*

Development and application of state-of-the-art quantum chemistry methods using the MRCC program package

Péter NAGY, Mihály KÁLLAY

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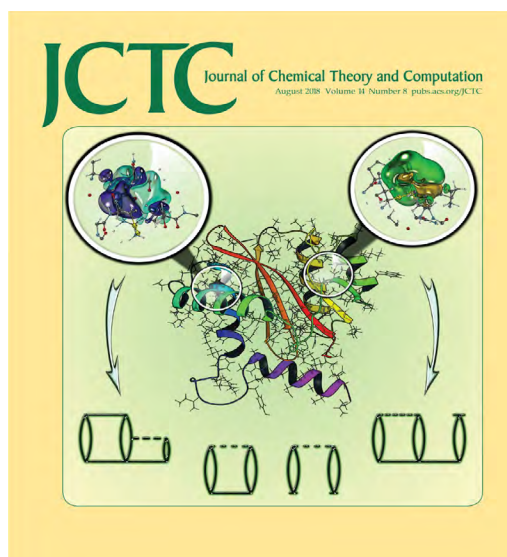
Atomistic simulation methods have become one of the top ten tools employed across all scientific disciplines to model processes in physics, (bio)chemistry, and materials science. Their main benefit is that atomic and molecular systems can be modeled using the fundamental laws of physics, such as quantum mechanics, electrodynamics, statistical mechanics, etc. to form ever more realistic computational representations supplementing experiments. Our group develops and employs quantum chemistry methods to solve quantum mechanical equations yielding predictive observable properties of molecules, such as reaction and interaction energies, molecular structure, or light-matter interaction properties.

The main difficulty lies in finding the balance between the computational cost and the accuracy of various models approximating the desired molecular properties. In practice, there are two main families of approaches incorporating the required quantum mechanical effects. Density functional theory (DFT) methods, often containing

Figure 1: *Record-sized catalytic domain of the HIV-1 integrase protein including 2380 atoms treated at the LNO-CCSD(T) level. Our Journal of Chemical Theory Computation cover page illustrates the main idea of LNO-CCSD(T) computations. ©American Chemical Society*

empirical parameters, are relatively affordable for routine chemical applications, but still have well-known difficulties in accurately modeling a number of quantities. On the other hand, first-principles wave function methods, such as the coupled-cluster (CC) approaches can be systematically improved to obtain sufficient accuracy, but they are often out of reach for molecules above 20-30 atoms, even with the largest supercomputers. Hence, extensive efforts are invested worldwide as well as in our group to combine the best of both, i.e., to improve the reliability of the faster DFT methods and to accelerate the accurate CC methods to be routinely affordable. Our developments take place in our quantum chemistry program package called MRCC (www.mrcc.hu) [1], which is open source for academic use and has more than 750 registered users.

Regarding DFT approaches, MRCC implements the most often used DFT methods and a number of unique variants developed in our laboratory. To improve the accuracy of DFT methods, we combine traditional DFT as well as wave function components. We have extended the most accurate rung of DFT approaches in several new directions [2] and also decreased their computational cost drastically [3] leading to their most efficient implementation currently available in any quantum chemistry code. We have also applied this line of combined DFT/wave function development to

excited states of molecules occurring upon certain light-matter interactions. This is a particularly challenging property for DFT methods, in which category our developments are currently the most accurate [4]. Moreover, we developed new ways to employ accurate wave function methods only for the most important, such as the chemically active part of a large molecule and treat the environment using cost-effective DFT methods [5].

We are also devoting extensive efforts to develop the wave function-based CC methods, as their accuracy has been repeatedly corroborated against experiments over the past three decades. One of the unique and most popular features of the MRCC program is its general order CC implementation [1]. These methods provide most of the highly-accurate thermochemical computational data for small but important molecules from the atmosphere to biomolecules [6]. Our implementation of the CCSD(T) variant of CC, generally regarded as the "gold standard" of quantum chemistry, is highly optimized for parallel execution on supercomputers and also holds the world record reaching up to 30-50 atoms due to its outstanding efficiency [7]. We are also pioneering various data-compression-, high-performance computing-, and physics-based techniques to accelerate the predictive CCSD(T) approach for even larger molecules relevant in modern (bio)chemistry (Fig. 1). Currently, our accelerated CCSD(T) code is the only one capable of providing sufficiently converged computations above 200-300 atoms, while our record-sized applications have recently surpassed the milestone of 1000 atoms (Fig. 2)[8].

Using our advanced programs in MRCC, we were able to effectively utilize the national level computation resources of KIFÜ. We are also thankful for the additional 7.4 and 10.9 million CPU core hours of computer time granted by the Partnership for Advanced Computing in Europe (PRACE) program due to the membership of KIFÜ in this useful resource exchange program. Our state-of-the-art methods have contributed, for instance, to the better understanding of environmentally-friendly organocatalytic reactions [9] and provided previously unattainable accuracy for the molecular interactions within large protein-ligand, amino acid-cation, as well as supramolecular complexes (Fig. 3)[10].
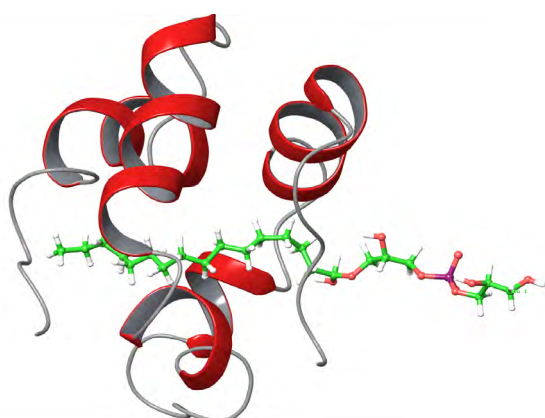

Figure 2: *Protein-ligand complex of a lipid transfer protein representing the largest ever converged CCSD(T) computation performed by our LNO method and the MRCC program. © AIP Publishing*
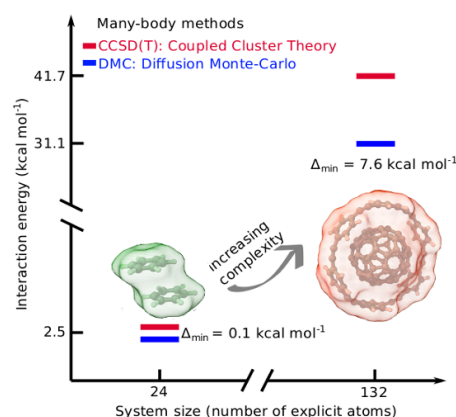

Figure 3: *Highly-regarded quantum Monte Carlo and CCSD(T) methods are in agreement for small molecular dimers (left), but the consensus is lost for some large supramolecular complexes revealed by our LNO-CCSD(T) method. [Nature Communications 12 3927 (2021)]*

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The atomic and electron structure of graphene superlattices

Péter SÜLE

Péter Süle, theoretician, senior research Fellow, Center for Energy Research (ELKH-EK), Dept. of Nanostructures. He obtained his PhD in Physics from the University of Debrecen (its predecessor, Lajos Kossuth University) in 1997. Postdoctoral researcher in Antwerp and Graz from 1997-2000. He has been a fellow at the Institue of Technical Physics and Materials Science (MFA) since 2000, and a Senior Fellow since 2005. Main research areas: density functional theory, high-temperature superconductivity, ion-beam physics, graphene nanostructures, molecular dynamics simulations.

In the course of our research, we study the dynamics of nanostructures at the atomistic level using molecular dynamics (MD) simulations (using mainly the LAMMPS software package). In addition, we also perform electronic structure calculations using density functional (DFT) codes (e.g. SIESTA, Quantum Espresso etc.). These calculations often require the use of supercomputers. The used program packages require a massively parallel MPI environment, large and fast access memory, moreover take advantage of the accelerating effect of auxiliary processors (GPU, XeonPhi).

Graphene is an allotrope of Carbon with one atomic layer thickness forming a two-dimensional layer. Research holds great promise for the electronic application of graphene but may be useful in other areas as well. This is because the ideal graphene has excellent properties: excellent electrical and thermal conductivity. Its good light transmission and photovoltaic properties make it suitable for use in solar panels. Furthermore, its mechanical properties also set a record: extremely light yet strong material (1 m2 sample weighs only 0.77 mg). Its tensile strength, on the other hand, is 1 TPa, 100 times stronger than a steel film of similar geometry. Graphene is the thinnest and strongest material currently known.

As a senior research fellow of the Department of Nanostructures in the Center for Energy Research (ELKH-EK), I have been intensively using KIFÜ's supercomputers for graphene research for the past 10 years. Most of the studies were mainly motivated by the problems raised by the experimental (scanning tunneling microscopy, STM) colleagues (led by L. Tapasztó, EK).
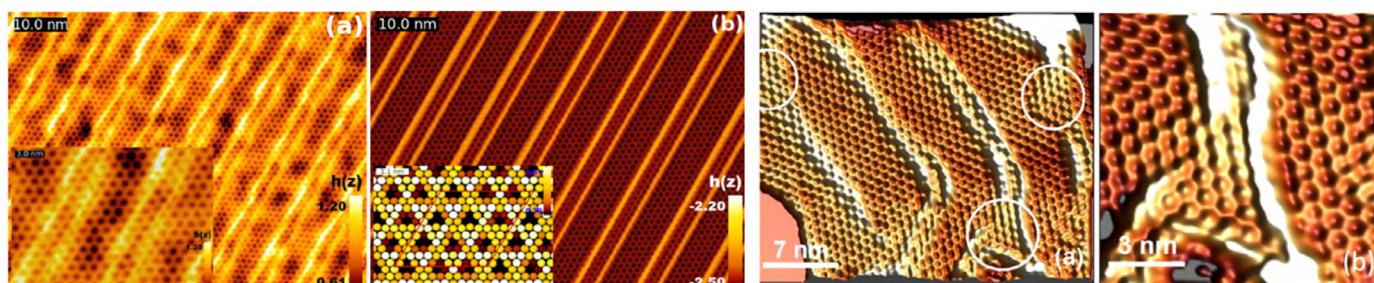

Figure 1: *Graphene on Au(111) support. Left panel: The various reconstructions (herringbone and concave Moiré superlattices) can be seen on graphene (a) and on Au(111)(b) as simulated by MD. The Insets show partly zoomed area (a) and concave imprinted periodic indentations on Au(111) as calculated by DFT (b). Panel on the right: Atomic resolution scanning STM image of the graphene nanomesh on Au(111) done by experimental colleagues. Periodic convex and concave Moiré superlattices are visible side by side.*

In one of our projects, we have shown that graphene protrudes and is indented in close proximity to each other on a gold support within a nano-sized area (see Fig. 1, left and right panels). Furthermore, it was found that graphene interacts weakly with the gold support to induce surface reconstruction on the gold surface.

That is, the deformations (morphology) of graphene appears as imprints on the surface of Au(111) (see Fig. 1(b)). The above surprising behavior was explained by the lattice mismatch at the interface and by the plasticity of the surface of Au(111). Another interesting finding is that graphene displays the specific so-called "herringbone" reconstruction of Au(111).

In another project [2], we investigated the electronic structural properties of sufficiently deformed graphene. Experimental colleagues called nano-scaled crumpled graphene was produced, which has then been shown to have surprising sensitivity when interacting with organic molecules (potential promising sensor application). We managed to model by DFT that the local density of states on the surface of the crumpled graphene (modeled with a nano-dome) changes significantly and becomes confined covering the entire surface of the dome with a characteristic dimension of about 5 nm diameter, and roughly 1 nm height (see Fig. 2(b)). Such a structural deformation forces charge carriers into closed orbits (pseudo-Landau levels) realizing spatially their confinement into the nanoscale protrusions. This system is suitable for a specific light-matter interaction that induces the collective oscillation of the electron system, giving rise to an intriguing type of quasi-particles named plasmons. In this way, it could be suitable for ultra-sensitive detection of specific molecules, for the construction of stable and highly sensitive sensors [2].
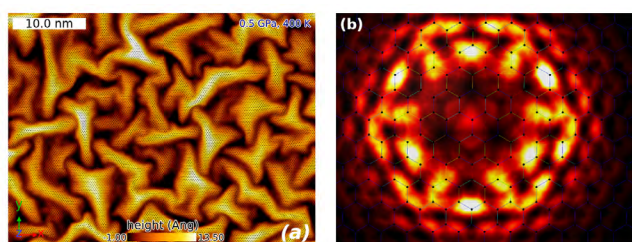

Figure 2: *(a) Nano-scale crumpled graphene as simulated by molecular dynamics. (b) The nanoscale confinement of electrons into the highest occupied pseudo-Landau level within the nano-dome. The spatial distribution of the local density of states on a graphene nano-dome as calculated by DFT. The curved honeycomb lattice of the graphene nano-dome is also shown.*

In other projects (highlighting only the most important ones) we have demonstrated that state-of-the-art molecular dynamics simulations, sometimes combined with ab initio DFT, provide useful information for the study of previously and only limitedly understandable and accessible processes and materials using the Hungarian supercomputer infrastructure [3-7]. Perhaps the most interesting of these works is the so-called nano-scale Moiré effect was studied for graphene-Cu(111) and Au(111) superlattices [4,5,7]. The Moiré effect is well known at the macroscopic level when photographing: Interference from two misoriented or different sized line grids is detected as an unwanted distortion effect on the developed photos. At the atomistic level, a similar phenomenon can be observed for superimposed atomic lattices, if they rotated only even at a small angle to each other and/or if the atomic grids are of different sizes. The elementary unit cell of these Moiré superlattices can be determined: however, as the coverage of the two grids changes as a function of the angle of rotation and/or lattice mismatch, the interaction between the layers is also tuned resulting in periodic morphological changes in the graphene layer (mostly periodically occurring convex protrusions)[1,3,5,6]. To accurately describe the interaction between the graphene and support layers, also we had to develop a new angular-dependent empirical interfacial potential [3,7].

Finally, perhaps it is worth mentioning two more ongoing works: simulations of ZrTe5 nanobubbles and nucleation in the iron melt. In one of these projects, a new angular-dependent force field was developed for ZrTe5, which is a promising topological insulator whose band structure is tuneable with deformation. With the new force-field, large-scale simulations were performed for nanobubbles of realistic size. The results show a bubble morphology that is in good agreement with the experiment (scanning tunneling microscopy measurements done by P. Nemes-Incze, EK). In another project, we study the crystallization and nucleation of liquids, with special regard to early nucleation (with L. Gránásy, Wigner). The results show early unprecedented hidden ordering and intriguing spatial inhomogeneity in the supercooled fluid.

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How can We Design Better Polymers with Supercomputers?

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Julie Mallouhi, Dániel Pecsmány, Edina Reizer,
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Computational Molecular Design Research Group / CoMoDe

CoMoDe is an interdisciplinary research group working at the intersection of chemistry, physics, and biology with the aim to design environmentally friendly materials. It belongs to the Institute of Chemistry and the Higher Education and Industrial Cooperation Centre at the University of Miskolc. Computational chemistry tools with the help of high-performance computing facilities are routinely applied by the members of CoMoDe in their research. The group's motto is "Nothing is Permanent Except Change".
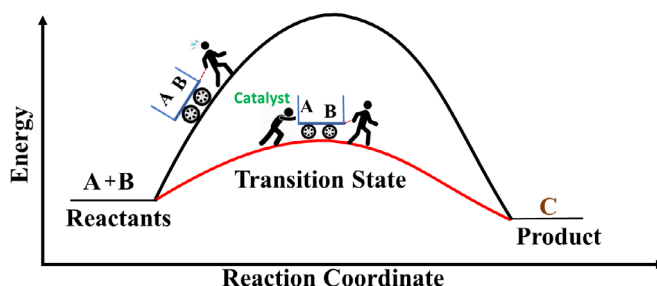
Polyurethane (PU) is one of the most versatile and unique polymer types being a part of our daily life and used in the industry for manufacturing a wide variety of products. It was developed by Otto Bayer and ranks among the most important breakthroughs in polymer science[1]. It can be found in different forms such as flexible and rigid foams, paints, coatings, adhesives, packaging, insulation, and synthetic fibers for clothing[2]. Above two million tons of various polyurethanes are synthesized every year in the European Union alone[3]. It is produced by reacting molecules carrying -NCO groups (isocyanates) with structures containing -OH groups (polyols), and the reaction result in the formation of multiple urethane linkage (–NH–COO–). The isocyanates and polyols are responsible for different properties of the polyurethane such as flexibility, and hardness of the final product[4].

As PU is widely used in many applications, and different synthetic procedures are applied to prepare them, therefore catalysts are important in the process of synthesizing the polymer. Catalysis plays a fundamental role in industrial chemical transformations and can expedite chemical reactions compared to catalyst-free systems (Figure 1).

Nowadays, catalysts are used in more than 90% of chemical and refining processes[5], and thus, the use of milder reaction conditions is possible. In polyurethane synthetic procedures, catalysts can increase the reaction rate, increase the production efficiency, promote the desired reaction and suppress the side reactions selectively. There are many types of catalysts used in polyurethane synthesis such as amine catalysts, organometallic compounds, organophosphorus compounds, inorganic salts and others. However, amine catalysts and organometallic compounds are the most common types used in urethane synthesis[6].

There are many research studies dealing with the effect of catalysts on urethane formation and the results prove that catalysts are key components of polyurethane synthesis, and significantly reduce the environmental

Figure 1. *Schematic representation of a reaction energy profile in the presence (red) and in the absence (black) of a catalyst.*

impact of chemical processes and the energy required to carry them out. Therefore, by designing better catalysts a more environmentally friendly polyurethane synthesis would be possible. To achieve this, first of all, the catalytic urethane formation has to be described at the molecular level.

High Performance Computing (HPC) facilities provided by the Governmental Agency for IT Development (KIFÜ) were applied to assess urethane formation with and without selected industrially important catalysts by the members of the Computational Molecular Design (CoMoDe) Research Group at the University of Miskolc. Phenyl isocyanate (PhNCO) and methanol (or butan-1-ol) were used as model reactants and the catalytic effect of different amine catalysts was described by using computational chemistry tools (Figure 2). More than 200 calculations have been carried out during the research project.
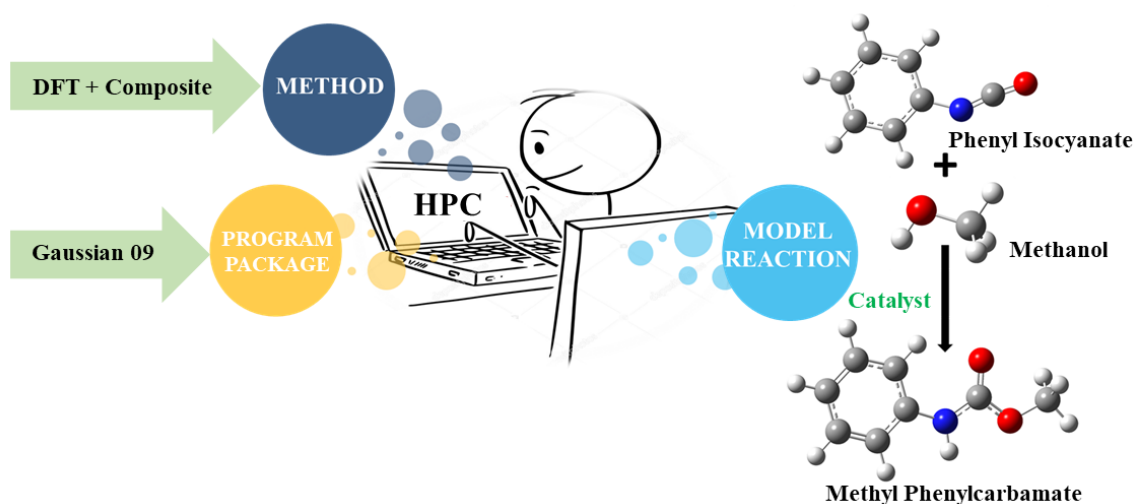

Figure 2. *Schematic representation of the applied computational procedure to study urethane formation.*

Based on the results, CoMoDe members have been able to propose a general urethane formation mechanism without and in the presence of the studied catalysts (Figure 3).
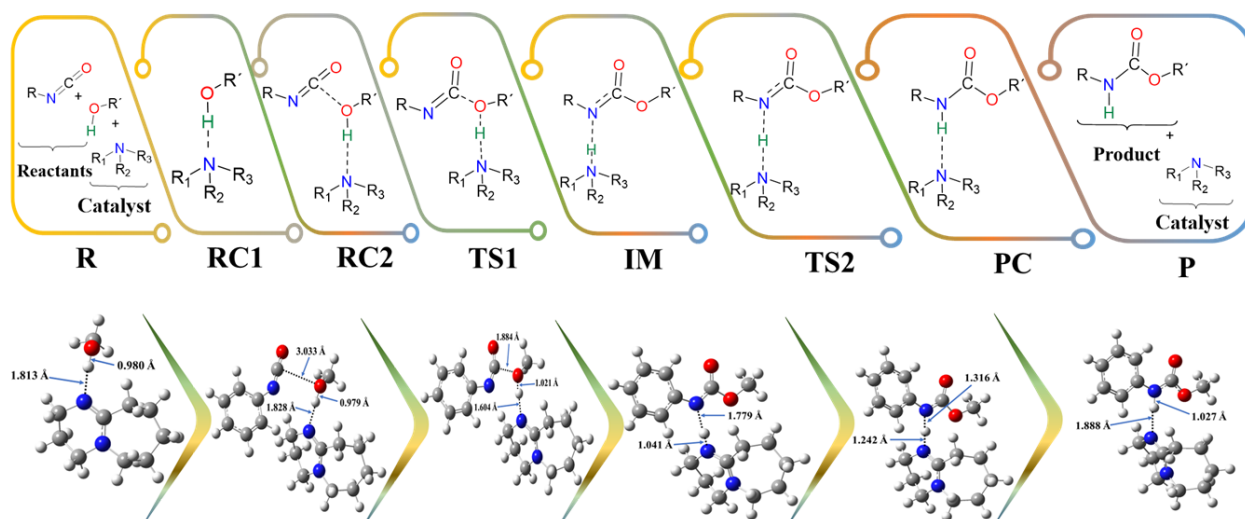

Figure 3. *Schematic representation of the proposed general urethane formation reaction (top). Optimized structures along the reaction pathway between phenyl isocyanate and methanol in the presence of a catalyst (1,8-diazabicyclo[5,4,0]undec-7-ene)(bottom), calculated at the BHandHLYP/6-31G(d) level of theory in acetonitrile at 298.15 K and 1 atm. R – reactant, RC – reactant complex, TS – transition state, IM – intermediate, and PC – product complex.*
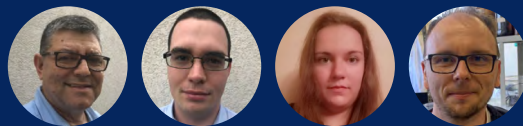
The results showed that the barrier height of the reaction significantly decreased (ΔE_0 > 100 kJ/mol) in the presence of the studied catalysts, which also proves their important effect on urethane formation. Thus, by adding catalysts to the system, the activation energy is significantly reduced, and urethane formation is promoted[7,8]. The molecular-level understanding of the catalytic urethane formation process will pave the way for the design and development of better catalysts and thus, more and more environmentally friendly polyurethane synthetic procedures will be developed in the near future.

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Superoxide dismutases and their mimics on HPC systems

The SOD project team

In the MTA-DE Redox and Homogenous Reaction Mechanisms Research Group at the University of Debrecen, the physico-chemical features of superoxide dismutase mimics are extensively studied. Superoxide dismutases (SODs, Figure 1) are a dedicated class of enzymes capable of catalyzing the decomposition reaction of superoxide anion which is one of the so-called reactive oxygen species (ROS) in the living systems. Recent studies highlighted that the overproduction of ROS can promote the progression of tumors due to the structural alteration of DNA and the inactivation of tumor suppressor genes. Thus, drugs for decreasing the concentration of ROS open new avenues for the treatment of cancer.[1] Moreover, the activities of SODs are often reduced in the early phase of cancer.[2] Therefore, a promising approach in human clinical medicine is the invention of new SOD mimics (ROS scavengers), particularly those that target cancer cells.
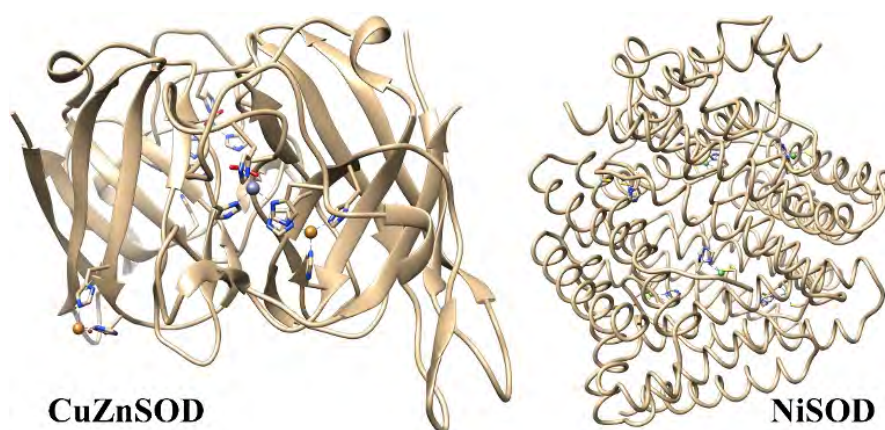

Figure 1. *Stereo ribbon diagram of CuZnSOD (PDB: 2APS) and NiSOD enzymes (PDB: 1T6U).*

In general, SODs and SOD mimetics usually contain a redox-active metal ion which accelerates the decomposition of ROS. Designing appropriate mimics with these metal ions is essential in order to model the SOD enzymes and to develop novel complexes. At this point, comprehensive thermodynamic and structural studies are essential in order to explore the intimate details of the formation of these complexes and theoretical chemistry helps to better understand such features.

In recent years, we have intensively studied the active site of the recently discovered nickel-containing SOD enzyme (NiSOD).[3-6] Our results unambiguously proved the high nickel binding affinity of the N-terminal part of the peptide which is the so-called NiSOD binding motif. Spectroscopic studies complemented by density functional theory (DFT) were used to identify the donor groups involved in the metal binding. Further studies were
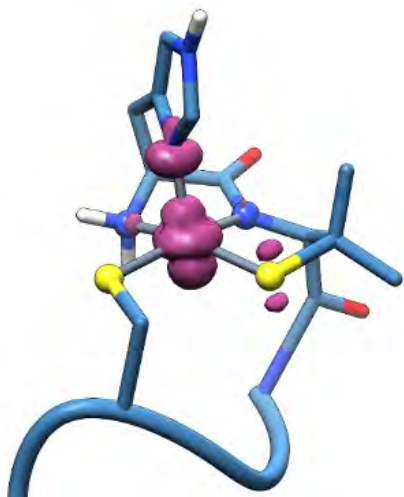
Figure 2. *The total spin density of the oxidized form of the metallopeptide mimicking the NiSOD binding motif computed at the DFT level of theory.*

focused on the SOD activity of these metallopeptides.[3,6] Therefore, several point mutations were applied in the native enzyme fragment and the results have shown that the presence of both cysteinyl residues are essential in the efficient degradation of superoxide ion.[4] Very recently, *D*-penicillamine, as a natural decomposition product of penicillin was incorporated into the peptide chain of the NiSOD binding motif. Full DFT and molecular dynamics methods were used to identify the donors both in the reduced and oxidized forms of the metallopeptide. Our kinetic data on the decomposition of superoxide anion unambiguously proved that the lifetime of the oxidized form of the metallopeptide can be altered by introducing electron donating substituents close to the catalytic center.[6] DFT methods provided further support to these observations (Figure 2).

While nickel SODs have been identified only in bacteria, similar enzymes containing copper, manganese and iron play significant roles in human bodies. Since the direct utilization of the native SOD enzymes as a pharmaceutical agent is not feasible due to its low membrane permeability, low molecular weight SOD mimics may act as an alternative to SOD in clinical treatments. In a quest for developing such compounds, we have used the pyridine-2,6-dicarboxamide platform which can be readily conjugated with different amino acids (Figure 3).[7] We have studied the coordination chemistry of these compounds and proved their high copper(II) binding affinity. SOD activity studies revealed that these complexes exhibit high SOD activity, and one of these new complexes possesses the best activity reported so far regarding open-chain copper(II) complexes. This is most probably due to the presence of tyrosine substituent which promotes the binding of the superoxide anion radical and the slightly distorted geometry around the copper center which probably favors the one-electron reduction of copper(II) to copper(I).

Finally, the results reported here are based on comprehensive investigations involving both experimental and computational techniques. The calculation of the electronic features of such compounds is not a trivial task, however, our results provide clear evidence for the benefits of using computational techniques in bioinorganic chemistry.
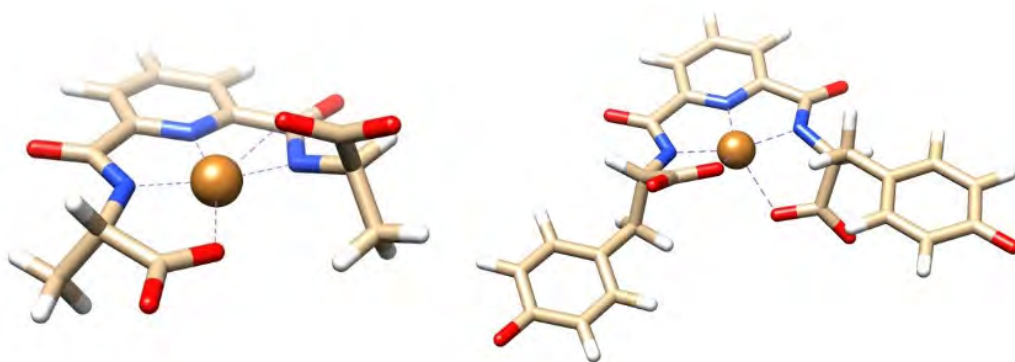

Figure 3. *DFT computed structures of novel copper-containing superoxide dismutase mimics.*

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Theoretical spectroscopy of qubits in solids

Ádám GALI

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We are living in the dawn of quantum computers, quantum communication and quantum sensors but the suitable platforms are still the subject of research, including solid-state defect qubits [1]. Ádám Gali's research group focuses the activities on the search, characterization and optimization of solid-state defect qubits by means of quantum mechanical simulations at the atomic scale. Qubits are the elementary units of quantum computers or, in general, quantum information processing. These two-level quantum mechanical systems can be often realized by electron and nuclear spins of point-like defects in solids [2]. Single-electron spins introduced by a certain defect in solid may be read out by optical means if a correlation exists between the fluorescence intensity and the spin state. The coherent superposition state of the electron spin can be achieved by applying an alternating magnetic field pulse in the microwave region. Since quantum processors require qubit registers with precise arrangement defect engineering at the atomic-scale could be a subject of investigation as well as the readout processes of the qubit and its manipulation by external perturbations such as magnetic and electric fields, strain and temperature. In all these thrusts, atomic scale quantum mechanical simulations can strongly contribute to discoveries and push forward quantum technology. Quantum mechanical simulations are running yet on classical computers. The computation of solid-state defect qubits is very demanding; therefore, massively parallel algorithms are employed using the high-performance computational facilities at KIFÜ.

The quantum mechanical calculations are based on Kohn-Sham density functional theory (KS-DFT) and beyond, including extensions towards many-body perturbation theory and wavefunction methods. In the last decade, Ádám Gali' group developed and implemented methods for theoretical magneto-optical spectroscopy to calculate the radiative, non-radiative and intersystem crossing rates of defects in solids which determine the readout fidelity and the sensitivity of qubit sensors [3, 4]. The implementations mostly rely on plane wave supercell KS-DFT codes which guarantee to assess the convergence of the results in many respects. In this case, the defects are modeled in a piece of the host crystal, called a cluster, and periodic boundary condition is applied at the edge the cluster building up a supercell that contains the crystal embedding the point-like defect (see Fig. 1).

Ádám Gali's group apply these methodologies to characterize and optimize the operation of known qubits and explore new ones for given quantum technology applications. Here we list only a few results that have been recently achieved either solely by the group or in collaboration with other research groups doing experiments.

One of the most successful defect qubits is the nitrogen-vacancy (NV) center in diamond (see Fig. 1). In NV center, the defect is negatively charged where the extra charge is donated by neighbor defects. NV center has a high spin $S=1$ electron spin and strongly fluoresces in the visible, thus it is also called color center in diamond. Recently, it has been shown (see references in Ref. [3]) that its electron spin can be read out in the photocurrent signal once an appropriate microwave field is sweeping during the photo-ionization of the defect. On the other hand, nuclear spins in diamonds are particularly attractive due to their long coherence time with respect to electron spins. The basic quantum processor unit – a single ^{14}N nuclear spin coupled to the NV electron – was read photoelectrically and thus operates in a manner compatible with nanoscale electronics. Our theory provided the

key ingredients for photoelectric quantum gate operations and readout of nuclear qubit registers. These findings could enable the development of electronic quantum processors based on the dipolar interaction of spin qubits placed at nanoscopic proximity [5].

Diamond is a brilliant but hard material to process. Therefore, Ádám Gali's group searched for alternative semi-conductors which can be readily processed and might be integrated into existing technologies of the electronics industry. One of the most promising candidates is silicon carbide (SiC). SiC may crystallize in such forms in which a single defect type could occur in multiple configurations with slightly different magneto-optical parameters that provide additional resources to pick up that configuration that suits the best for the given application [6]. In collaboration with researchers at Hefei University, we studied one configuration of a silicon-vacancy qubit in SiC and found an unconventional readout process, the so-called anti-Stokes excitation, where the exciting laser has lower energy than the emitted photons. We found that the spin coherence properties are the same as those of Stokes excitation, but with a signal contrast that is around three times greater. To illustrate the enhanced spin readout contrast under anti-Stokes excitation, Ádám Gali provided a theoretical model. We demonstrated that the current anti-Stokes excitation ODMR approach has promising applications in quantum information processing and quantum sensing [7].

Recently, color centers in silicon, a traditional semiconductor for the electronics industry, have been found and isolated as single defects with relatively strong emissions which may act as qubits [1]. In particular, the so-called G center in silicon was first isolated. We identified the exact microscopic structure of the G photolu-minescence center in silicon by first-principles calculations including a self-consistent many-body perturbation method, which is a telecommunication wavelength single-photon source. The defect constitutes of C_sC_i carbon impurities in its C_s-Si_i-C_s configuration in the neutral charge state (see Fig. 2), where s and i stand for the respective substitutional and interstitial positions in the Si lattice. We revealed that the observed fine structure of its optical signals originates from the athermal rotational reorientation of the defect. We attributed the monoclinic symmetry reported in optically detected magnetic resonance measurements to the reduced tunneling rate at very low temperatures. We discussed the thermally activated motional averaging of the defect properties and the nature of the qubit state [8].

Two-dimensional materials are also emerging solid-state platforms to host qubits [1]. Ádám Gali's group achieved breakthroughs in the identification of single spin defects in hexagonal boron nitride (hBN) and tungsten disulfide (WS$_2$). A group at Stuttgart University observed single spin defects in hBN [9]. By accurate calculation of the interaction of the electron spin and the surrounding nuclear spins, the carbon defect substituting the boron was identified as the origin of the qubit in hBN [9, 10]. We propose carbon as a qubit in another two-dimensional material, WS$_2$. A milestone has been recently achieved by demonstrating that a single defect, a carbon atom substituting sulfur atom in single-layer WS$_2$, can be engineered on-demand at atomic size level precision, which holds a promise for a scalable and addressable unit. It is an immediate quest to reveal its potential as a qubit. To this end, we determined its electronic structure and optical properties from the first principles. We identified the fingerprint of the neutral charge state of the defect in the scanning tunneling spectrum. In the neutral defect, the giant spin-orbit coupling mixes the singlet and triplet excited states resulting in phosphorescence at the telecom band that can be used to read out the spin state, and coherent driving with microwave excitation is also viable (Fig. 3). Our results establish a scalable qubit in a two-dimensional material with a spin-photon interface at the telecom wavelength region [11].
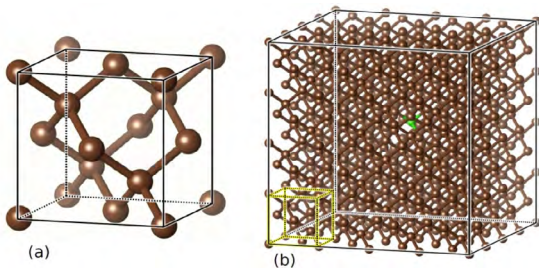

Figure 1: *Supercell modeling of point defects in crystals on the example of nitrogen-vacancy defect in diamond. (a) Unit cell of diamond. (b) Supercell of diamond. The host crystal contains 512-atom, whereas one carbon atom is removed (vacancy) and one carbon atom is substituted by a nitrogen atom (green ball) to construct the defect.*
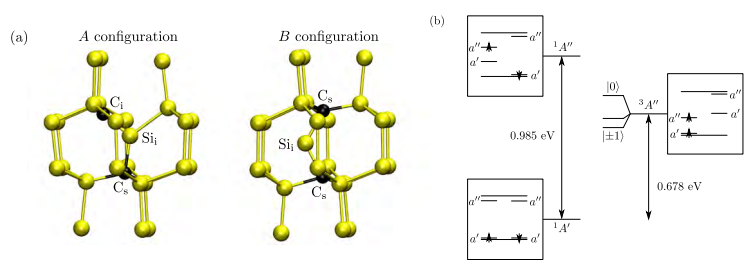

Figure 2: *(a) Zoom in the microscopic origin of the G-center in silicon (B configuration) and (b) its electronic structure*
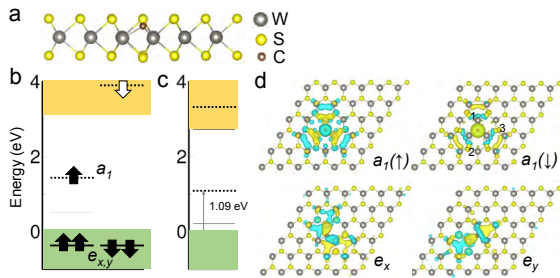
Figure 3: *The proposed C-defect qubit in WS$_2$: (a) geometric and (b) electronic structures without and with spin-orbit coupling as well as (c) the plotted wavefunctions*
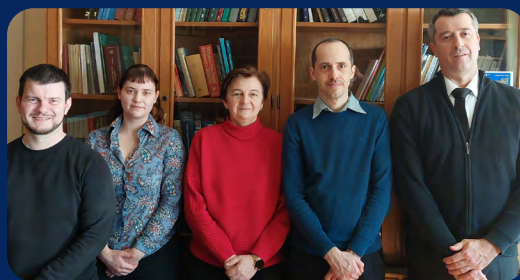
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Stereochemistry of synthetic and natural derivatives and mechanism of domino cyclization reactions

From left to right: Tibor Kovács, Aliz Rimóczi, Anikó Borbás, Attila Mándi and Tibor Kurtán.

The Syntreak HPC group

Prof. Tibor Kurtán (group leader), Dr. Attila Mándi, Ms. Aliz Rimóczi, Mr. Tibor Kovács (Dept. of Organic Chemistry, University of Debrecen) and Prof. Anikó Borbás (Dept. of Pharmaceutical Chemistry, University of Debrecen). We started to use the Hungarian supercomputers in 2008 and continued in 2011 with the novel infrastructure. In the last ten years, more than 110 ESI papers were published with the efficient support of the NIIF(I)/KIFÜ. The studied derivatives were isolated or synthesized by domestic (Debrecen, Szeged, Budapest, Pécs) and international partners (Germany, China, Australia, Japan).

A significant portion of pharmacologically active derivatives is chiral and thus exists in the form of at least two stereoisomers. The stereoisomers or enantiomers can exploit markedly different pharmacodynamic or pharmacokinetic behavior, which can be reflected in different bioactivities. One enantiomer (eutomer) of the chiral drug may match precisely the active site of the chiral receptor protein, while the other (distomer) cannot bind to the active site so efficiently or binds to a different site, which results in reduced activity, no activity or in some cases even different or harmful effect. Therefore, it is a fundamental aim to elucidate the absolute configuration for potentially bioactive compounds. The configurational assignment of chiral drug molecules is the final step of their structural elucidation and it is required for the exploration of their structure-activity relationship. The absolute configuration of optically active stereoisomers can be determined by means of chiroptical methods, which are based on the interaction of the sample with the left and right circularly polarized components of the linearly polarized light. These methods consist of but are not limited to the specific rotation (OR), electronic circular dichroism (ECD) and vibrational circular dichroism (VCD).[1] While the OR has a long history and the ECD method has been known and applied for more than 70 years, the VCD techniques are relatively new ones and they came to practice in the past 20 years. The VCD method measures circular dichroism in the infrared (IR) region and hence deals with the excitations of the vibrational energy levels instead of those of the electron energy levels in the ECD. The IR and VCD transitions can be calculated easier than the ultraviolet (UV) and ECD ones and the larger number of bands in the IR and VCD spectra carries more structural information.[2] On the other hand, the ECD method is more sensitive when having strong chromophores in the vicinity of the chirality centers and thus it can be utilized efficiently for much smaller sample amounts (down to a few µg) which is usually the case for natural products.[3] Since these chiroptical methods are often complementary, their combined application is recommended for a safe configurational assignment.[4]

Our ongoing computational projects aim to elucidate stereochemistry (absolute and relative configuration and conformation) of natural and synthetic derivatives and to explore mechanisms and stereoselectivity of domino cyclization reactions.[5] Since chiroptical data depend on both the configuration and conformation of the studied molecule, it is inevitable to do a thorough conformational analysis and test the level dependency for a safe assignment, which is rather CPU time-consuming for large and flexible derivatives. Due to the versatile planar structures and different properties of the studied compounds, there is no superior general computational approach or combination which can be applied automatically for all the cases. The ideal combination of experimental and computational methods is to be decided case-by-case depending on the structure and experimental spectroscopic data of the studied molecule and it may also require re-iteration on the basis of the

preliminary calculation results. For flexible derivatives, the way how we generate the initial conformers is crucial for the outcome. In order to reduce the required CPU time, we are pushed to apply truncation of the structure,[6] reclustering of computed conformational isomers,[7] solid-state experimental methods[8] or simplified calculation methods such as sTDA,[4c,9] however, one has to test and find out the scope and limitations of these approaches.

The relative configuration of complex natural products containing multiple non-correlated stereogenic elements quite often cannot be elucidated unambiguously by means of experimental methods. The solid assignment of the relative configuration of multiple stereogenic elements is inevitable for the successful application of chiroptical spectroscopy to determine the absolute configuration since ECD and VCD approach usually cannot distinguish more than four stereoisomers. We utilize calculations of the ^{13}C and ^{1}H NMR chemical shifts, interatomic distances for NOE correlations as well as three-bond homo- and heteronuclear coupling constants supplemented with statistical analysis to aid the assignment of the relative configuration.[10] The combined application of these methods often provided a surprising result suggesting that the initially proposed relative configuration or even the planar structure requires revision.

Regarding the calculation of the reaction mechanism, the order and activation parameters of the elementary steps in domino cyclization sequences were determined and the observed stereoselectivities were interpreted. In the following, a few selected examples are discussed on the stereochemical analysis of natural products.

The endophytic fungus *Trichocladium* sp. was cultured

Figure 1. Selected examples of natural products, the stereochemistry of which were elucidated by the aid of DFT / TD-DFT / sTDA calculations of chiroptical properties.

on various mediums and in co-cultivation with *Bacillus subtilis* leading to the isolation of several new cytotoxic natural products including bismacrolactone **1** with four chirality centers (Figure 1).[11] A combination of TDDFT-ECD, TDDFT-SOR, DFT-VCD and DFT-NMR calculations were applied to determine the absolute and relative configurations of **1**. The relative configuration of the C-13 chirality center could not be deduced from experimental data due to the conformational flexibility of the fourteen-membered ring. ECD calculations performed on the (2*R*,8*R*,10*R*,13*R*) and (2*R*,8*R*,10*R*,13*S*) epimers showed a slight preference for the (2*R*,8*R*,10*R*,13*R*) epimer (Figure 2a).
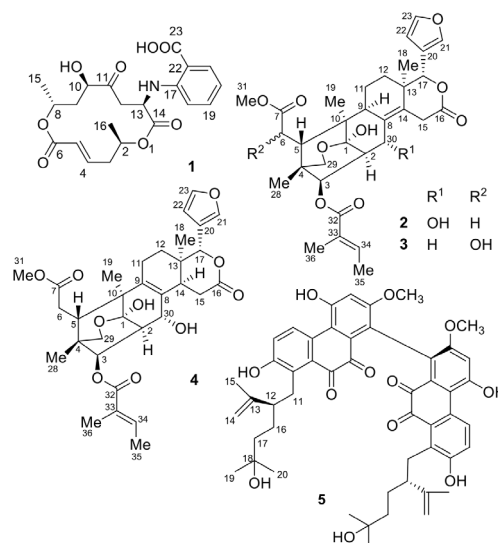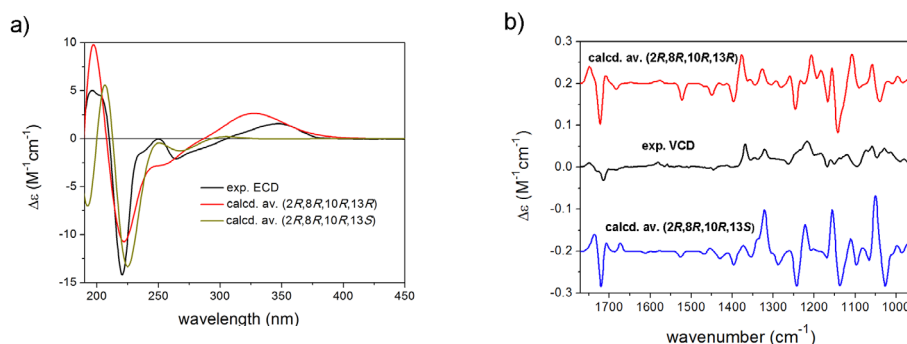

Figure 2. Experimental a) ECD spectrum of **1** in MeCN and b) VCD spectrum of **1** in CDCl$_3$ compared with the Boltzmann-weighted calculated ECD and VCD spectra, respectively, of the two possible stereoisomers.

VCD calculations also supported the (2*R*,8*R*,10*R*,13*R*) stereoisomer when analyzing the similarity indexes but the other epimer gave also acceptable agreement (Figure 2b). The ^{13}C NMR shift calculations and coupling constant calculations corroborated the results of the VCD and ECD calculations allowing unambiguous elucidation of the absolute configuration.

TDDFT-ECD calculations were utilized to explain the mirror image or different ECD spectra of previously reported homochiral natural products thaigranatins A–E and granatumin L, the simple comparison of which would have resulted in a wrong stereochemical conclusion (Figure 1 and 3).[12] The configurational assignment was confirmed independently and geometrical parameters of the chromophores governing the ECD spectra were identified in

the structurally related natural products by analyzing the ECD spectra and geometries of the low-energy computed conformers obtained by different methods. Different conformations of the furan-2-yl-δ-lactone subunit were found responsible for the mirror image ECD spectra of the homochiral thaigranatins C–E (**2–4**). DFT ^{13}C NMR chemical shift calculations and DP4+ analysis were performed on the C-6 epimers of thaigranatin D (**3**), which together with the ECD calculation, could determine the absolute configuration of the previously unknown chirality center C-6 as (*R*).

Leucobryn A (**5**), a 9,10-phenanthrenequinone dimer containing a stereogenic biaryl axis, were isolated from the moss *Paraleucobryum longifolium*.[4c] It contained both axial and central sterogenic elements due to the hindered rotation along the biaryl axis, which were a challenge to determine simultaneously even by the combination of chiroptical methods. Due to the large size of the molecule, the ECD approach affording the axial chirality were performed with the simplified sTDA method (Figure 4), while the central chirality elements were assigned by TDDFT-SOR calculations. Leucobryn A represents the first 9,10-phenanthrenequinone dimer with antiproliferative activity, the monomers of which are linked through their C-8 atoms.
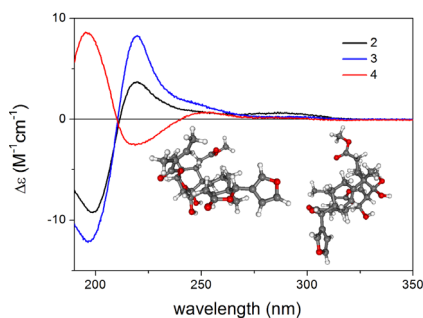

Figure 3. *Experimental ECD spectra of **2–4** in acetonitrile and comparison of the low-energy solution conformer of **4** (left) with the higher-energy one.*
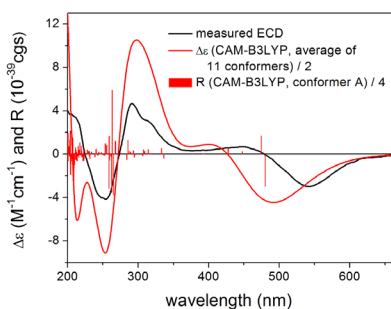
Figure 4. *Comparison of the experimental ECD spectrum of **5** in acetonitrile compared with the sTDA spectrum of (aS,12R,12′R)-**5**. Bars represent the rotational strength values of the lowest-energy conformer.*

Gibbosols A, B (**6, 7**) and benthol A (**8**), super-carbon-chain compounds, were isolated from marine dinoflagellates by our Chinese collaborating partners (Figure 5).[10] Despite the sophisticated chemical fragmentations applied in both cases, experimental NMR studies could not elucidate the stereochemistry of all the chirality centers. In order to determine the relative and absolute configuration in the problematic fragments, ^{13}C DFT-NMR chemical-shift calculations aided by DP4+ statistical analysis were applied for different stereoisomers. Benthol A displayed potent antimalarial activity against *Plasmodium falciparum* 3D7 parasites.
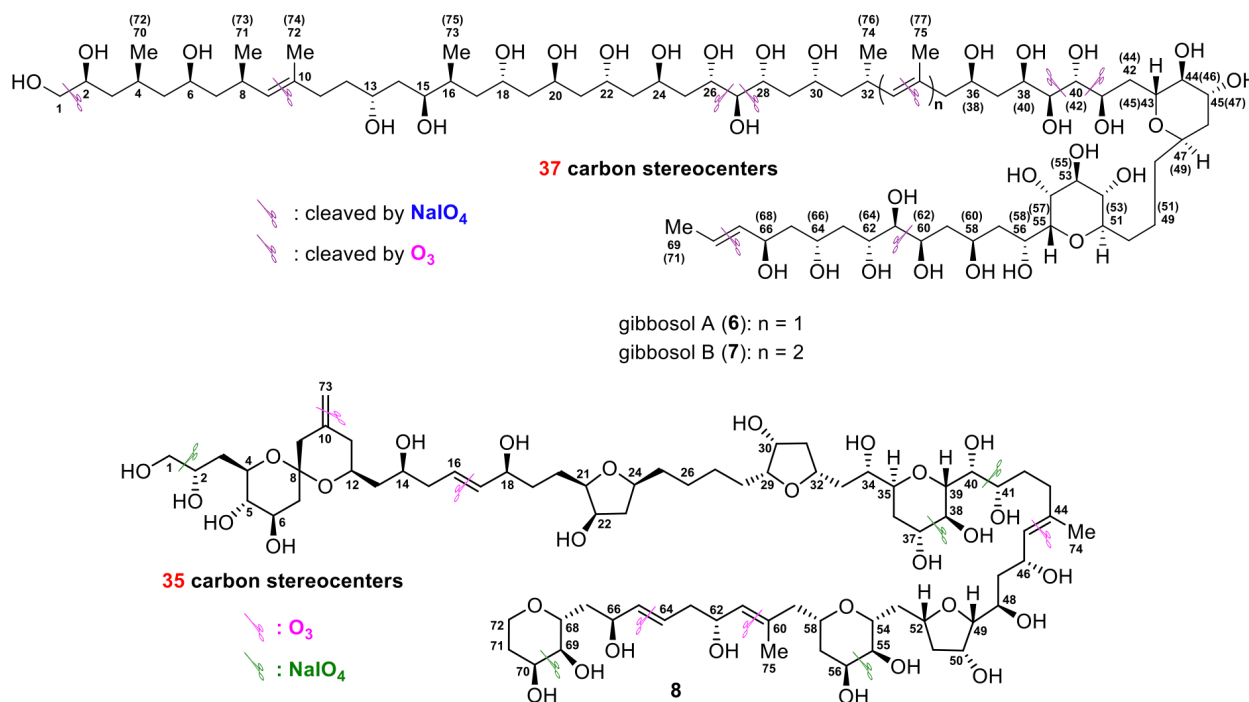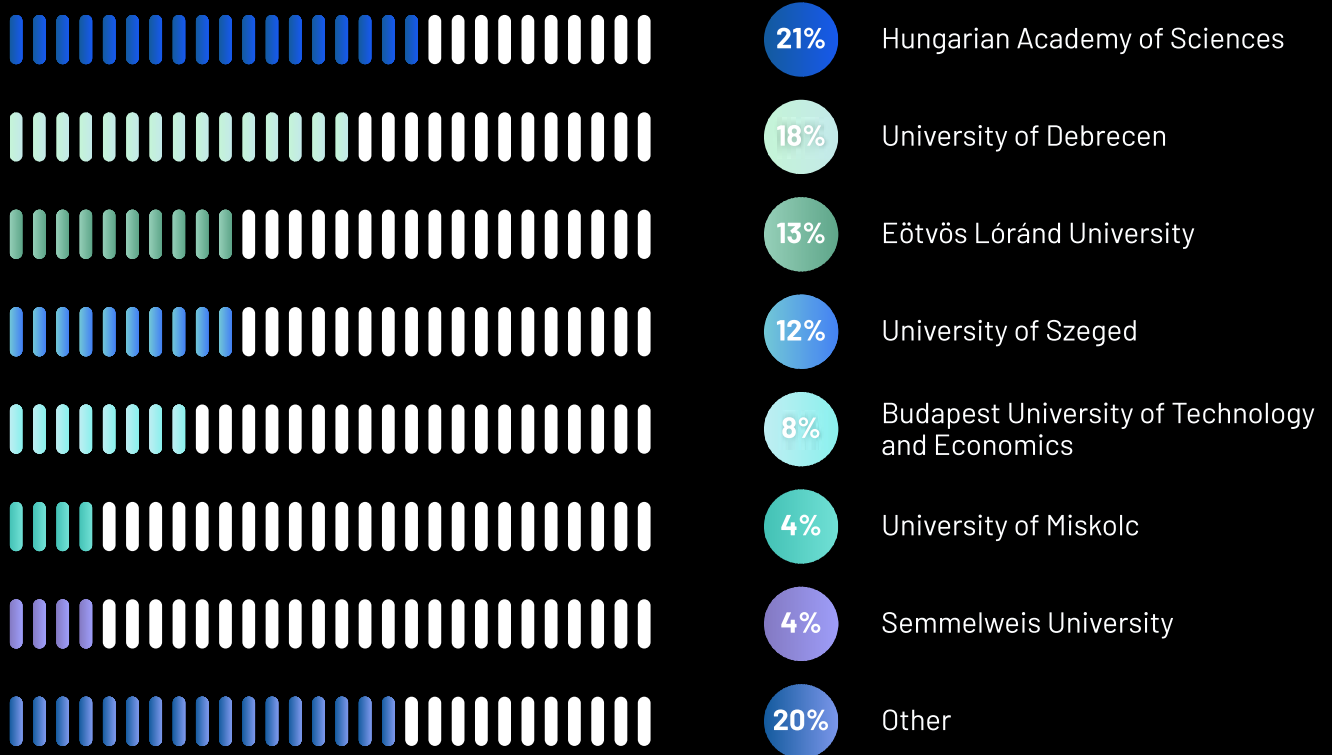

Figure 5. *Structures and fragmentation of super-carbon-chain marine natural products **6-8**, the stereochemistry of which were elucidated by the aid of DFT NMR calculations.*

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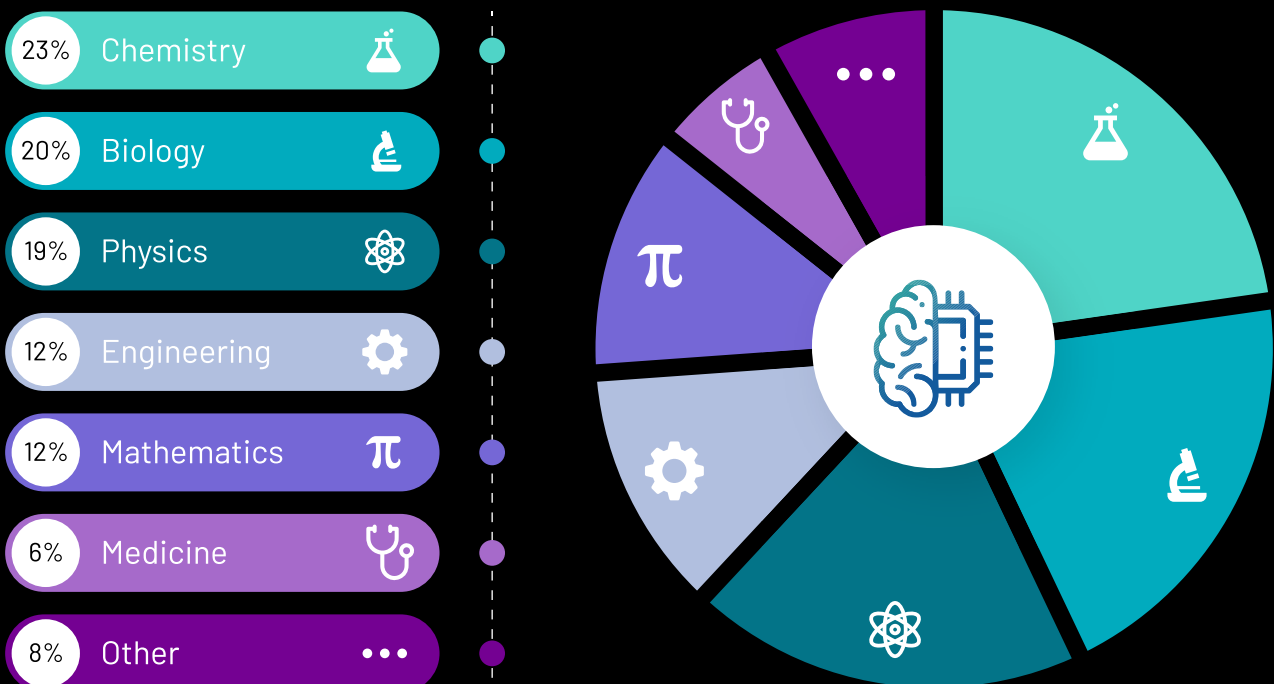[12] A. Mándi, J. Wu, T. Kurtán, RSC Adv. 2020, 10, 32216-32224.
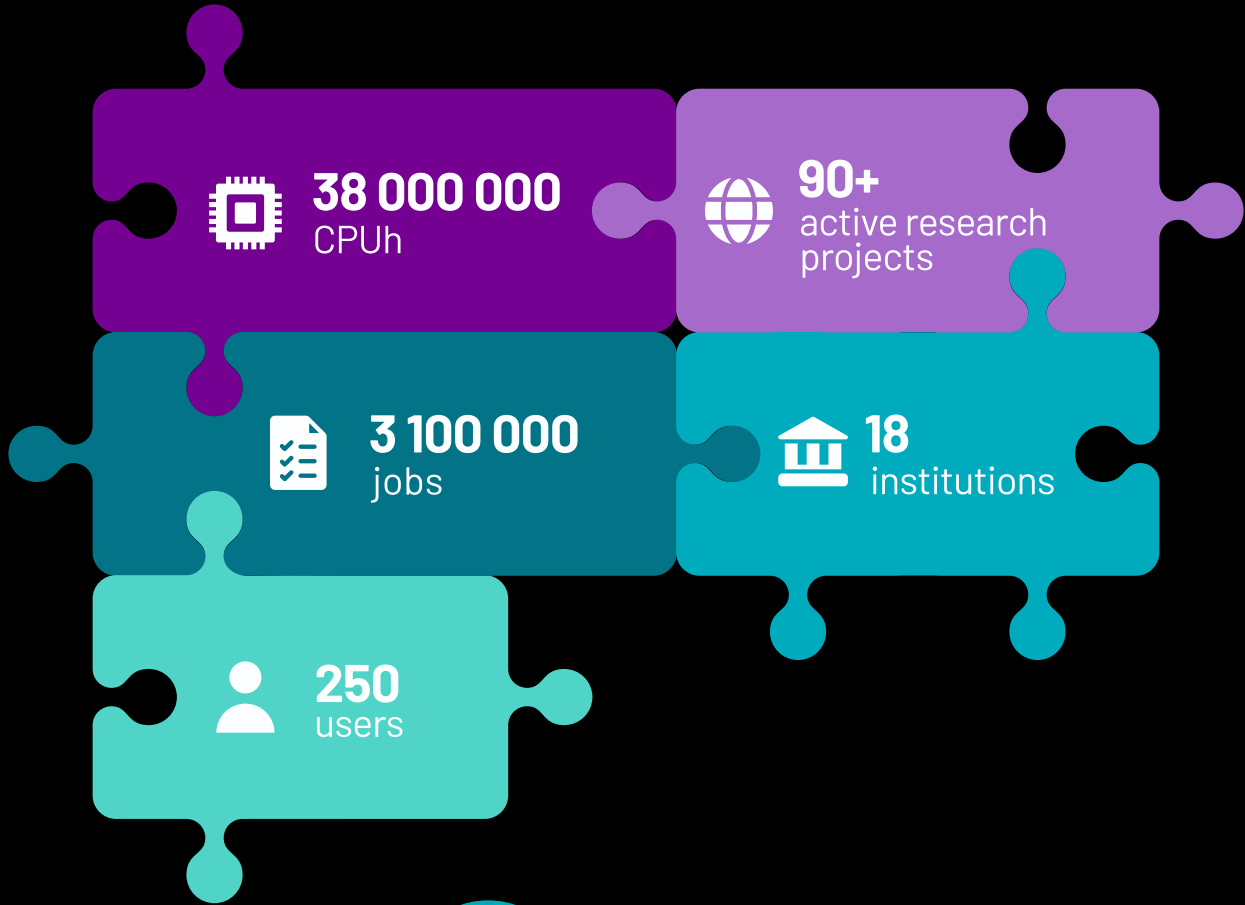
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