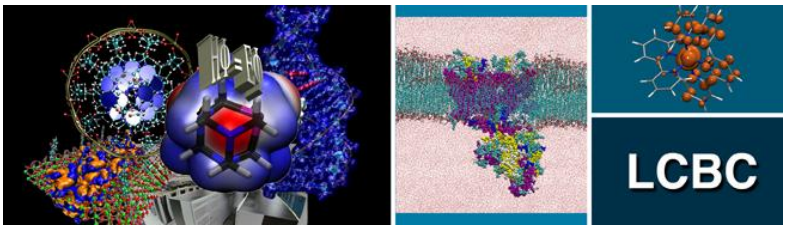
Computational chemistry across scales and disciplines: celebrating the 60th birthday of Ursula Röthlisberger



October 1 - 3, 2024
CECAM-HQ-EPFL, Lausanne, Switzerland

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1. Description

Computational chemistry is one of the core disciplines of CECAM, and its progress in the last decades, as well as its contributions to the advancement of science and society, has been remarkable. This progress stems from two main aspects: first, by being intrinsically connected with the development in computer hardware and software solutions, it has dramatically benefitted by the continuous growth in computing power; second, because of the unique role of chemistry as the “central science”, it has extended its influence and impact in many neighboring disciplines.

In this symposium, in the occasion of her 60th birthday, we want to celebrate the achievement of Prof. Ursula Röthlisberger, an outstanding computational chemist that has forecast and actively contributed to advance the computational chemistry field in its many disguises. On the one hand, she has strongly contributed to methodological developments in quantum chemistry, most notably of hybrid (quantum mechanics/molecular mechanics, QM/MM) approaches, also overseeing their implementation into widely used computational chemistry software packages. On the other hand, she has applied computational chemistry methods to significantly advance our mechanistic understanding of several processes in disciplines as diverse as biomedicine, material science, or organic chemistry. For her discoveries, she has been awarded numerous prizes, including the Ruzicka Prize at ETH in 2001 and the Dirac Medal by the World Association of Theoretical and Computational Chemists (WATOC), and she has contributed to the community in her role of associate editor of the American Chemical Society Journal of Chemical Theory and Computation and as a fellow of the American Association for the Advancement of Science. Over the years, she has also actively mentored and supported many young women scientists, and more than 20 of her lab alumni now hold independent PI position in three continents. For this workshop/symposium, by bringing together her mentors, alumni and longstanding collaborators, we plan to reminisce over the last three decades of computational chemistry and look forward to the exciting challenges ahead.

2. Program

Day 1 - Tuesday October 1st 2024

- 08:45 to 09:15 - Registration

Chair: Alessandra Magistrato

- 09:15 to 09:30 - Opening CECAM Director
- 09:30 to 10:00 - **Michele Parrinello**

  A new approach to the rare event problem
- 10:00 to 10:30 - **Vassily Hatzimanikatis**

  Models, databases and computational methods for analysis, synthesis and design in synthetic metabolism
- 10:30 to 11:00 - Coffee break
- 11:00 to 11:30 - **Carme Rovira**

  Discovering glycosylation mechanisms
- 11:30 to 11:50 - **Marko Mladenovic**

  Fully-atomistic modelling of valence change memory cells
- 11:50 to 12:10 - **Ariadni Boziki**

  Simulations of vibrational spectra of molecular crystals
- 12:10 to 13:30 - Lunch

Chair: Michele Cascella

- 13:30 to 14:00 - **Michael Grätzel**

  From molecular photovoltaics to perovskite solar cells, a tribute to the seminal computational contributions of Prof. Ursula Roethlisberger and her team
- 14:00 to 14:30 - **Carla Molteni**

  Exploring phase transformations in nanomaterials
- 14:30 to 15:00 - Coffee break
- 15:00 to 15:30 - **Ali Alavi**

  How should one deal with large open-shell systems?
- 15:30 to 15:50 - **Anatole von Lilienfeld**

  Quantum machine learning in chemical space
- 15:50 to 16:10 - Coffee break
- 16:10 to 16:40 - **Matteo Dal Peraro**

  Integrating simulations and experiments to understand aerolysin pore-forming toxins
- 16:40 to 17:00 - **Enrico Tapavicza**

  Computational design of light-driven molecular nanomotors
- 18:00 to 00:00 - Social dinner

Day 2 - Wednesday October 2nd 2024

Chair: Paolo Carloni

- 09:30 to 10:00 - **Michael Klein**

  Molecular simulation and the precursors of nanotechnology
- 10:00 to 10:30 - **Daniel Sebastiani**

  Explicit configurational entropy of mixing in MD simulations
- 10:30 to 11:00 - Coffee break
- 11:00 to 11:20 - **Marta A. S. Perez**

  TCRpcDist: A cutting-edge in silico algorithm for advancing cancer
- 11:20 to 11:40 - **Polydefkis Diamantis**

  Effect of single-point mutations on the redox chemistry of DNA
- 11:40 to 12:00 - **Mauricio Coutinho Neto**

  Challenges of lipopeptide simulations: Matching experimental data with simulation abilities
- 12:00 to 13:30 - Lunch

Chair: Pablo Campomanes

- 13:30 to 14:00 - **Paul J. Dyson**
- 14:00 to 14:20 - **Marialore Sulpizi**

  Exploring nucleotides complexes in solutions from spectroscopy and ab initio simulations
- 14:20 to 14:40 - **Roberto Lins**

  Engineering proteins towards diagnostics and therapy of viral infections
- 14:40 to 15:10 - Coffee break
- 15:10 to 15:40 - **Modesto Orozco**

  Multiscale modeling of nucleic acids
- 15:40 to 16:00 - **Marc-Etienne Moret**

  Nickel/olefin cooperation for H2 activation
- 16:00 to 16:30 - Coffee break
- 16:30 to 17:00 - **Marco De Vivo**

  Cutinase proteins to process non-natural polyesters
- 17:00 to 17:20 - **Swarnendu Bhattacharyya**

  Understanding all x-ray attosecond transient absorption spectroscopy of liquid water
- 17:20 to 17:40 – **Liz Brunk**

  Machine learning of three-dimensional protein structures to predict the functional impacts of genome variation
- 17:40 to 19:00 - Aperitif

Day 3 - Thursday October 3rd 2024

Chair: Ute Röhrig

- 09:30 to 10:00 - **Mark E. Tuckerman**
  Topological crystal structure prediction
- 10:00 to 10:20 - **Leonardo Guidoni**
  The reaction mechanism of water splitting in natural photosynthesis
- 10:20 to 10:50 - Coffee break
- 10:50 to 11:10 - **Michel A. Cuendet**
  Allosteric mechanisms in proteins mapped as thermodynamic coupling landscapes
- 11:10 to 11:30 - **Negar Ashari Astani**
  Computational chemistry with quantum computational models
- 11:30 to 11:50 - **Simone Meloni**
  Does nanoconfined water looks like bulk water?
- 11:50 to 12:00 - Closing Word

3. Abstracts

A new approach to the rare event problem

Michele Parrinello
Istituto Italiano di Tecnologia, Italy

Molecular dynamics simulation is arguably one of most powerful tools since the study of material science, chemistry, biology and physics problems. Yet its scope is limited by computer power limiting the accuracy of the model used to describe the system and the time scale of the simulation. This latter limitation is particularly severe since many interesting phenomena take place over time scales that cannot be sampled in brute force simulations. The solution to this problem has occupied the minds of simulators for several decades now and much progress has been made. Much progress has been made with methods that identify the slowest degrees of freedom of the system and find ways of accelerating their sampling. However, as the complexities of the system studied increases, we find necessary to move to a more probabilistic global description of the rare event rather than focusing one's attention on specific degrees of freedom. Thus, we focus our attention on the committer a quantity that given two states A and B gives the probability that a trajectory started a configuration x ends in B without having first passed by A. We show how this quantity can be calculated using a variational principle due to Kolmogorov and how this approach allows rare events to be analyzed in exquisite detail. From the information thus gathered better catalysts or more potent drugs can be designed. We believe that our approach goes a long way towards the solution of the rare event problem.

Allosteric mechanisms in proteins mapped as thermodynamic coupling landscapes

Michel A. Cuendet
Swiss Institute of Bioinformatics, Switzerland

Going beyond the usual two-state models of allostery, we introduce a statistical mechanical formalism to describe the coupling between two collective variables that represent key conformational changes in a protein, such as ligand binding and activation. We show that allosteric coupling is best represented as a two-dimensional thermodynamic coupling function (TCF). This TCF can be approximately decomposed in terms of specific energy terms, which reveals quantitative insights into the allosteric mechanism at play. To illustrate the use of TCF analysis, we show how allosteric coupling in the alanine dipeptide molecule contributes to the overall shape of its Φ/Ψ free energy surface. We then showcase a fast version of the TCF analysis to decompose allosteric coupling based on coarse-grained Gaussian Network models. To demonstrate applicability to large physiologically-relevant biomolecular systems, we combined the TCF formalism and a Markov state model analysis of the human dopamine transporter (hDAT), revealing a non-trivial thermodynamic coupling landscape between the sodium release and intracellular gating steps. These examples illustrate the power of TCF analysis to reveal new mechanistic understanding of protein function.

Challenges of lipopeptide simulations: Matching experimental data with simulation abilities

Mauricio Coutinho Neto, Pedro Tendrih Sodré
Universidade Federal do ABC, Brazil

Lipopeptides are amphiphilic molecules made of short peptides with lipid chains linked to their backbones. They self-assemble, forming peptide functionalized supramolecular structures with different topologies. Their structure allows for a wide range of uses, including catalysis, membrane-disruptive antibiotics, and molecular sensors.
During this presentation, I will discuss two applications of lipopeptides that have been investigated using both experimental and theoretical methods. The initial application investigates how self-assembly affects the stereoselectivity of aldol catalyzed reactions using proline-containing lipopeptides. By employing Density Functional Theory and Molecular Dynamics simulations, we demonstrated the crucial role of the catalytic phase generated by the aggregate in attaining a high level of reaction

selectivity. The second application explores how theory can be used to uncover the fundamental interactions involved in the detection mechanism of a lipopeptide based pesticide sensor. In addition, I will present an evaluation of the difficulties associated to lipopeptide simulations.

*[1] P. Sodré, A. Aguilar, W. Alves, M. Coutinho-Neto, RSC Adv., **14**, 21035-21046 (2024)*

Computational chemistry with quantum computational models

Negar Ashari Astani
Amirkabir University of technology, Iran

As we push the boundaries of what classical computers can achieve, the emergence of quantum computers offers a transformative opportunity. By leveraging the principles of quantum mechanics, these technologies promise to tackle the complex, high-dimensional problems that have long been beyond reach just as Feynman envisioned in 1982. Different quantum computational models tackle electronic structure problems with distinct algorithms and techniques, each optimized for their unique strengths and operational characteristics. This presentation explores various encoding protocols for representing the molecular Hamiltonian across different quantum computational models.

Computational design of light-driven molecular nanomotors

Enrico Tapavicza
University of Regensburg, Germany

Light-driven molecular nanomotors (MNMs) convert light into mechanical energy. Due to their temporal and spatial controllability, MNMs have several potential applications in biomedical sciences, including drug delivery and permeabilization of membranes [1]. Improving their efficiency requires optimization of various molecular properties. Above all, a high product quantum yield (PQY) [2] for the photochemical isomerization that drive the conversion of photon energy into mechanical work is needed. This typically goes in hand with a high absorption cross section. Due to improved tissue penetration, near-IR light is the desired source of energy. However, due to the excitation energy required to drive the isomerization, this often requires usage of two-photon excitation. Based on quantum chemistry and ab initio non-adiabatic molecular dynamics, I will report efforts to design new MNMs with improved PQY, one- and two-photon absorption cross sections. To allow screening of a large number of molecular candidates, machine learning methods for the prediction of excited state properties [3, 4] take a crucial role in this development.

*[1] V. García-López, F. Chen, L. Nilewski, G. Duret, A. Aliyan, A. Kolomeisky, J. Robinson, G. Wang, R. Pal, J. Tour, Nature, **548**, 567 (2017)*
*[2] T. Thompson, E. Tapavicza, J. Phys. Chem. Lett., **9**, 4758 (2018)*
*[3] R. Ramakrishnan, M. Hartmann, E. Tapavicza, O. von Lilienfeld, The Journal of Chemical Physics, **143** (2015)*
*[4] E. Tapavicza, G. von Rudorff, D. De Haan, M. Contin, C. George, M. Riva, O. von Lilienfeld, Environ. Sci. Technol., **55**, 8447 (2021)*

Cutinase proteins to process non-natural polyesters

Marco De Vivo
Istituto Italiano di Tecnologia, Italy

In our lab, we study enzymatic catalysis, with the aim of disclosing mechanistic insights potentially useful for drug discovery and computer-aided enzyme design. Here, I will present recent efforts in dissecting biocatalytic approaches to address the plastic problem, which has received considerable attention in recent years due to its promise to meet the challenge of a circular plastic economy in an environmentally friendly manner. Protein engineering of natural cutinases, for example, is explored to improve the enzyme activity towards non-natural polyester. In this context, I will present our classical molecular dynamics (MD) and QM (DFT/B3LYP)/MM simulations (QUICK code, available in AMBER) used to dissect the mechanism of hydrolysis of polybutylene succinate (PBS) by Aspergillus oryzae cutinase. We plan to extend this computational approach to investigate the hydrolytic reaction mechanism of other polyesters. Eventually, the mechanistic insights provided by our atomistic simulations will aid the design of enzyme variants with improved activity toward non-natural polyesters.

Discovering glycosylation mechanisms

Carme Rovira
University of Barcelona, Spain

Carbohydrate-active enzymes, such as glycoside hydrolases and glycosyltransferases, constitute the main machinery for the degradation, synthesis and modification of carbohydrates in Nature. These enzymes have a myriad of industrial and biotechnological applications, ranging from biofuel production to biotherapeutics. Understanding how carbohydrates are processed by enzymes, identifying the itineraries that the sugar units follow during catalysis can inform the design, synthesis and application of new drugs and chemical probes in glycobiology and immunology. In this talk I will show how computer simulation, in particular QM/MM codes developed in the group of Ursula Röthlisberger, can help to understand how these enzymes work.

Does nanoconfined water looks like bulk water?

Simone Meloni
University of Ferrara, Italy

A lot is known about the properties of bulk water: its phase diagram, including non-trivial features, such as the so-called Wisdom line, other thermodynamic properties (e.g., isothermal compressibility and thermal expansion coefficient), its transport properties and much more, though the debate about its anomalies has kept (and is keeping) the scientific community for more than 50 years. Water in its liquid or gasses/vapors can be confined within porous media of various size, shape and “chemistry” (more or less hydrophilic/phobic). How does its properties change under confinement? For example, does water under extreme confinement, contained within (strictly) nanometric or sub-nanometric pores, still present distinguished liquid and gas phases? Under this extreme confinement, when the number of water molecules in contact with the solid surface is comparable with the those in the “bulk”, is it still meaningful to speak about the properties water or one should rather consider the fluid/solid composite as a single system? Additionally, can one possibly tune the properties of the fluid (or composite) by changing the properties of the confining environment? Finally, can one exploit the (possibly tunable) properties of confined water for technological applications? In my talk I will try to address some of these questions and present the challenges ahead of us.

*[1] S. Merchiori, A. Le Donne, J. Littlefair, A. Lowe, J. Yu, X. Wu, M. Li, D. Li, M. Geppert-Rybczyńska, L. Scheller, B. Trump, A. Yakovenko, P. Zajdel, M. Chorążewski, Y. Grosu, S. Meloni, J. Am. Chem. Soc., **146**, 13236 (2024)*

[2] S. Merchiori, A. Donne, R. Bhatia, M. Alvelli, J. Yu, X. Wu, M. Li, D. Li, L. Scheller, A. Lowe, M. Geppert-Rybczynska, B. Trump, A. Yakovenko, M. Chorążewski, P. Zajdel, Y. Grosu, S. Meloni, Small (2024)

Effect of single-point mutations on the redox chemistry of DNA

Polydefkis Diamantis
Hengrui Europe Biosciences, Switzerland

Experimental investigations have suggested that DNA-mediated charge transfer can be exploited by base excision repair enzymes for the recognition of defect DNA bases[1,2]. For this to be a possibility, the redox properties of defect DNA fragments must be substantially different from their native counterparts. To explore this, a systematic computational investigation was carried out to compute the redox properties of native and defect DNA systems differing by a single 8-oxoguanine (8-oxoG) base replacing a native guanine (G) base[3-5]. The size of the systems ranged from single bases and nucleotides to nucleosome core particles (NCPs). Findings showed that DNA-mediated hole transport is a much more likely candidate for 8oxoG detection than excess electron transport.
In addition, the replacement of G by an 8oxoG in large bare DNA fragments and NCPs, leads to an increase of the oxidation potential by 1 eV, while relative differences in structural reorganization upon oxidation are negligible between the native and defect fragments. This strongly suggests that 8oxoG recognition occurs based on mainly electrochemical criteria and is in favor of a DNA-mediated hole transfer mechanism for the recognition of DNA lesions arising from oxidative damage.

*[1] A. Boal, J. Barton, Bioconjugate Chem., **16**, 312 (2005)*
*[2] A. Boal, J. Genereux, P. Sontz, J. Gralnick, D. Newman, J. Barton, Proc. Natl. Acad. Sci. U.S.A., **106** (2009)*
*[3] P. Diamantis, I. Tavernelli, U. Rothlisberger, J. Chem. Theory Comput., **15**, 2042 (2019)*
*[4] P. Diamantis, I. Tavernelli, U. Rothlisberger, J. Chem. Theory Comput., **16**, 6690 (2020)*
*[5] M. Kılıç, P. Diamantis, S. Johnson, O. Toth, U. Rothlisberger, J. Chem. Theory Comput., **19**, 8434 (2023)*

Engineering proteins towards diagnostics and therapy of viral infections

Roberto Lins
FioCruz Fundacao Osvaldo Cruz, Brazil

The escalating global epidemics of flavivirus infections underscores the urgent need for accurate diagnostics and innovative therapeutic strategies. Leveraging on data and biological samples from our own clinical studies, the talk will describe our efforts to identify key epitopes and to engineer proteins tailored for both diagnosis, and treatment of Zika and Dengue infections. A machine learning-based model to predict absolute protein-protein binding free energies as a strategy towards high-throughput protein engineering will also be presented. I will also take this opportunity to verse on the, indirect but crucial, influence of Prof. Ursula Roethlisberger on establishing the field of computational protein engineering in Brazil.

Explicit configurational entropy of mixing in md simulations

Daniel Sebastiani, Till Hanke, Luisa Upterworth
Martin-Luther University Halle, Germany

The equilibrium entropy of mixing of a multi-component system of particles is a simple expression of the molar fractions for the equilibrium state. However, its instantaneous values for transient (non-equilibrium) states cannot be calculated directly from the particle coordinates so far. We propose a simple expression for the configurational entropy of mixing based solely on the set of instantaneous coordinates, suitable for the on-the-fly determination of the degree of mixing along a molecular dynamics trajectory.

Exploring nucleotides complexes in solutions from spectroscopy and ab initio simulations

Marialore Sulpizi[1], Emma Rossi[2], Achintya Kundu[3], Alberta Ferrarini[2], Thomas Elsaesser[3]
[1]Ruhr University Bochum, Germany
[2]University of Padova, Italy
[3]Max-Born-Institut Für Nichtlineare Optik und Kurzzeitspektroskopie, Berlin, Germany

Despite their fundamental relevance in biological processes and their applications in synthetic chemistry, elucidating the structure and dynamics of nucleotides complexes remains a non trivial task because of the presence of charges, highly polarizable species, solvent and conformational degrees of freedom.
Here I will address the characterization of adenosine triphosphate (ATP) -Zn complexes in a joint computational and experimental effort. We combine experimental measurements of the IR absorption spectra of ATP in water both in the absence and presence of Zn^{2+} with computed IR spectra from AIMD simulations of methyl triphosphate (MTP), a simplified model for ATP.
Performing accurate band assignments and structural characterizations, we show that water-triphosphate and metal-triphosphate interactions influence both frequency and coupling of asymmetric stretching of phosphate groups. The comparison between experimental and simulated spectra permits to identify the coordination modes of the ATP-Zn^{2+} complexes predominantly present in solution and to achieve a molecular understanding of the blueshift of the spectrum induced by the formation of the complex.
In the second part I will discuss how to overcome some limitation of the *ab initio* computational approach with the use of machine learning (ML) potentials, which permits to extend the range the applicability of such expensive methods to more realistic timescale. In particular, the conformational space of adenosine monophosphate (AMP) in solution is presented as a first test case, paving the way to more complex investigations.

Exploring phase transformations in nanomaterials

Carla Molteni
King's College London, United Kingdom

Nanocrystals show a wealth of distinctive behaviors with respect to their bulk counterparts, which can be tuned by varying their size, shape and surface. These include the way they respond to applied pressure and tensile stress, transforming from the original crystalline structure to new ordered or disordered phases. Of particular technological and fundamental interest are nanocrystals of tetrahedrally coordinated materials, such as Si, Ge, CdSe and CdS, which can be driven by pressure toward highly coordinated crystalline or amorphous phases, and of TiO_2, which may show ferroelectric behavior. To characterize the mechanisms of these phase transformations and explore the optical and electronic properties of the resulting systems, we have used a series of simulation techniques of different resolution, including density functional theory, molecular dynamics and metadynamics, and developed specific protocols for nanomaterials under pressure. We have focused, in particular, on the interplay between amorphization and crystallization, the emergence of metallic phases, piezochromic effects for pressure sensing, and the localization of soft modes that may trigger coherent phase transformations.

From molecular photovoltaics to perovskite solar cells, a tribute to the seminal computational contributions of prof. ursula roethlisberger and her team

Michael Grätzel
Swiss Federal Institute of Technology, Lausanne, Switzerland

TBA

Fully-atomistic modelling of valence change memory cells

Marko Mladenovic
ETH Zurich, Switzerland

We present a fully-atomistic theoretical framework to model valence change memory (VCM) cells. The model consists of three steps: (1) calculating the activation energies of relevant chemical processes using Density Functional Theory (DFT) calculations, (2) performing Kinetic Monte Carlo (KMC) simulations to obtain the structure of the conductive filament at given voltage and temperature, and (3) performing Quantum Transport calculations to obtain the conductance and the current through the device. [1] The model successfully emulates the switching mechanism in VCM cells based on the creation and rupture of the conductive filament made of oxygen vacancies. Furthermore, we demonstrate that the current flows through uncoordinated hafnium atoms neighboring oxygen vacancies. A newer version of the model includes the effects of Joule heating, allowing for a more realistic description of the resistive switching, closer to the experimental data. Finally, we apply the model to study some distinctive types of switching occurring in VCMs, such as interface-type switching in SrTiO3-based memristors and unipolar switching in NiO-based memristors.

*[1] M. Kaniselvan, M. Luisier, M. Mladenović, ACS Nano, **17**, 8281 (2023)*

How should one deal with large open-shell systems?

Ali Alavi
Max Planck Institute for Solid State Research, Germany

TBA

Integrating simulations and experiments to understand aerolysin pore-forming toxins

Matteo Dal Peraro
EPFL, Switzerland

Evolution has found countless ways to transport material across cells and cellular compartments separated by membranes. Protein assemblies are the cornerstone for the formation of channels and pores that enable this regulated passage of molecules in and out of cells, contributing to maintaining most of the fundamental processes that sustain living organisms.
Using integrative structural biology, i.e. combining molecular modeling and simulations along with biochemical and cryo-EM analysis, we have revealed the structure and assembly mechanism of one of the most studied bacterial pore-forming toxins, namely aerolysin from A. hydrophilia, recently obtaining its highest resolution structure at 2.2 Å by cryo-EM in nanodiscs.
Leveraging this structural and functional understanding, we have been able to characterize its properties as a molecular sensing device that can accurately discriminate nucleic acids and peptides, as well as detect post-translational modifications associated with validated biomarkers of neurodegenerative diseases. The sensitivity of aerolysin pores makes the ideal for developing the next generation of sensor devices for single-molecule proteomics and analytical chemistry.

Machine learning of three-dimensional protein structures to predict the functional impacts of genome variation

Elizabeth Brunk
ATOSIM Msc, United States

Research in the human genome sciences generates a substantial amount of genetic data for hundreds of thousands of individuals, which concomitantly increases the number of variants of unknown significance (VUS). Bioinformatic analyses can successfully reveal rare variants and variants with clear associations with disease-related phenotypes. These studies have had a significant impact on how clinical genetic screens are interpreted and how patients are stratified for treatment. There are few, if any, computational methods for variants comparable to biological activity predictions. To address this gap, we developed a machine learning method that uses protein three-dimensional structures from AlphaFold to predict how a variant will influence changes to a gene's downstream biological pathways. We trained state-of-the-art machine learning classifiers to predict which protein regions will most likely impact transcriptional activities of two proto-oncogenes, nuclear factor erythroid 2 (NFE2L2)-related factor 2 (NRF2) and c-Myc. We have identified classifiers that attain accuracies higher than 80%, which have allowed us to identify a set of key protein regions that lead to significant perturbations in c-Myc or NRF2 transcriptional pathway activities.

Models, databases and computational methods for analysis, synthesis and design in synthetic metabolism

Vassily Hatzimanikatis
EPFL, Switzerland

Metabolic engineering, synthetic biology, and management of metabolic networks in health, environmental, and nutrition sciences involve the design, analysis, retrofitting, and repair of genome-scale metabolic networks through the manipulation of enzyme activities and cellular processes. Two of the central problems in the studies of metabolism are the expansion of our current knowledge of biochemical reactions and compounds and the identification of targets for manipulating metabolism with the minimum possible impact on cells physiology. We will present and discuss our work in addressing one of these two problems using concepts and methods from chemoinformatics, chemical reaction engineering, and process systems engineering.
We will present and discuss the development of BNICE.ch, a computational framework for design, evaluation, ranking and visualization of the promising *de novo* pathways for several applications ranging from metabolic gap-filling to metabolic engineering and drug design.

BNICE.ch has several components that are integrated in a computational framework, namely: a database of generalized enzymatic reaction rules, integrated biological and chemical databases, metabolic network generation and pathway enumeration algorithms, and several cheminformatics and bioinformatics tools for the pathway feasibility studies.
We used BNICE.ch for the development of ATLAS of biochemistry, a database of all the biochemically plausible reactions between compounds reported to occur in living organisms. ATLAS uses KEGG as the reference database with 16,000 metabolites and 10,000 reactions and it contains more than 130,000 new reactions. The mining of ATLAS will undoubtedly offer new opportunities for the design of synthetic pathways and metabolic engineering.

Molecular simulation and the precursors of nanotechnology

Michael Klein
Temple University, United States

The year 1964 was notable not only for dramatic political events, but also because of significant advances in the sciences, as well as important concomitant developments in the arts. Two decades later, the initial steps towards Feynman's prescient vision of nanotechnology, were realized. The pivotal invention of the scanning tunneling microscope in 1981 by Binnig & Rohrer at IBM Zurich Research Lab, was awarded the 1986 Nobel-Physics Prize. The 1985 discovery of fullerenes by Curl, Kroto and Smalley, which received the 1996 Nobel-Chemistry Prize, spawned the discovery of nanotubes, and set the stage for the resurgence of graphene. In parallel, molecular self-assembly, and molecular nanotechnology, emerged as vibrant areas for research. Using selected examples, my talk will review how seminal developments in 1964, along with subsequent advances in molecular simulation during the 1980's and 1990's, contributed to advancing nanoscience and nanoengineering research.

Multiscale modeling of nucleic acids

Modesto Orozco
IRB Barcelona, Spain

Nucleic acids are a paradigmatic example of multiscale systems, where time scales can move from femtosecond to minutes and space scales from Angstrom to meters. I will summarize recent advances in our group in developing a bulk of methodology able to jump among scale providing a holistic picture of nucleic acids structure, dynamics and functionality.

Nickel/olefin cooperation for H2 activation

Marc-Etienne Moret, Maria Sansores-Paredes, Martin Lutz
Utrecht University, Netherlands

Understanding the fundamental mechanisms underlying the activation of chemical bonds is essential to design the catalysts of the future. The activation of H2 by transition metals (M) to form reactive M–H bonds is a key step for ubiquitous catalytic reactions such as (asymmetric) hydrogenations, olefin hydroformylation, and other reductions. This reaction typically involves either H–H oxidative addition to form two M–H bonds or deprotonation of a transient molecular hydrogen complex (nonclassical hydride, M–H2).1 In this contribution, we present experimental and computational evidence for a distinct mechanism involving direct transfer of a hydrogen atom from a M–H2 complex to a metalbound olefin (Ligand to Ligand Hydrogen Transfer, LLHT).2,3 Anchoring a C=C double bond to a nickel center in a "pincer" design allows the observation of both an olefin–Ni–H2 complex and the corresponding alkyl–Ni–H complex resulting of H–H activation in rapid equilibrium. The potential of this H2 activation step for homogeneous catalysis is demonstrated using alkyne semihydrogenation as a probe reaction. Experimental and computational mechanistic investigations support the central role of Ligand-to-Ligand Hydrogen Transfer steps.

*[1] G. Kubas, Chem. Rev., **107**, 4152 (2007)*
*[2] M. Sansores-Paredes, M. Lutz, M. Moret, Nat. Chem., **16**, 417 (2023)*
*[3] R. Perutz, S. Sabo-Etienne, A. Weller, Angew. Chem. Int. Ed., **61** (2021)*

Quantum machine learning in chemical space

Anatole von Lilienfeld
University of Toronto, Canada

Many of the most relevant observables of matter depend explicitly on atomistic and electronic structure, rendering physics based approaches to chemistry and materials necessary. Unfortunately, due to the combinatorial scaling of the number of chemicals and potential reaction settings, gaining a holistic and rigorous understanding through exhaustive quantum and statistical mechanics based sampling is prohibitive --- even when using high- performance computers.
Accounting for explicit and implicit dependencies and correlations, however, will not only deepen our fundamental understanding but also benefit exploration campaigns (computational and experimental). I will discuss recently gained insights from my labs elucidating such relationships thanks to supervised machine learning.

Simulations of vibrational spectra of molecular crystals

Ariadni Boziki
University of Luxembourg, Luxembourg

Molecular crystals are extensively used as active pharmaceutical ingredients and in other sectors, such as food, agriculture, and polymers. A major challenge in these industries, particularly pharmaceuticals, is the existence of multiple crystal forms (polymorphs) for the same compound. The physico-chemical properties, including thermal stability, solubility and dissolution rate, can dramatically vary between polymorphs, significantly impacting the drug efficacy. Thus, accurately predicting the correct polymorph of a compound is a critical goal.
THz spectroscopy is valuable in this endeavor, as each polymorph's unique spectral fingerprint aids in their identification. However, deciphering the vibrational spectra of molecular crystals poses a significant challenge. Assigning peaks to specific vibrational modes typically requires experience and chemical intuition, but the complexity of these spectra often makes such assignments impractical. Quantum chemistry methods have proven reliable in accurately simulating the vibrational spectra.
In this context, I will introduce TheSeuSS, an automated computational platform that efficiently simulates IR, Raman and THz spectra for both periodic and non-periodic systems at DFT and DFTB levels of theory. TheSeuSS also provides an accurate description of intermolecular forces, crucial for molecular crystals as their molecules are held together by weak intermolecular forces. Our user-friendly platform allows users with varying expertise to perform THz spectra simulations, facilitating efficient and accurate high-throughput screening of multiple polymorphs, significantly contributing to the broader efforts in crystal structure prediction studies. By drawing comparisons and highlighting the synergies between these two areas of research, we demonstrate how a fundamental understanding of structure-property relationships can lead to innovative design principles, tailored for specific applications.

TCRpcDist: A cutting-edge in silico algorithm for advancing cancer

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The emergence of immunotherapy stands as a pivotal advancement in modern medicine, particularly within the domain of oncology. Despite notable progress, further enhancements in immunotherapeutic strategies necessitate the development of robust in silico algorithms capable of surmounting existing limitations. In response to this imperative, our laboratory has pioneered the creation of TCRpcDist—a novel and structure-based algorithm for calculating T-cell receptor (TCR) Physico-Chemical distances. Leveraging metrics associated with molecular interactions executed by key residues within the TCR, TCRpcDist demonstrates unparalleled efficacy in determining antigen specificities of orphan tumor-infiltrating lymphocytes in cancer patients—a critical endeavor in contemporary immunotherapies [1]. By integrating TCRpcDist with a Tumor Reactive Predictor, we have identified clinically relevant TCRs for personalized T-cell Therapy [2].

Ongoing investigations are exploring the potential transferability of the TCRpcDist approach to elucidate antibody specificities—a pivotal pursuit in immunotherapy development. Soon, TCRpcDist will be accessible as a web service, facilitating widespread access to its capabilities within the scientific community.

[1] M. Perez, J. Chiffelle, S. Bobisse, F. Mayol-Rullan, M. Bugnon, M. Bragina, M. Arnaud, C. Sauvage, D. Barras, D. Laniti, F. Huber, M. Bassani-Sternberg, G. Coukos, A. Harari, V. Zoete, Advanced Science (2024)

[2] R. Pétremand, J. Chiffelle, S. Bobisse, M. Perez, J. Schmidt, M. Arnaud, D. Barras, M. Lozano-Rabella, R. Genolet, C. Sauvage, D. Saugy, A. Michel, A. Huguenin-Bergenat, C. Capt, J. Moore, C. De Vito, S. Labidi-Galy, L. Kandalaft, D. Dangaj Laniti, M. Bassani-Sternberg, G. Oliveira, C. Wu, G. Coukos, V. Zoete, A. Harari, Nat. Biotechnol. (2024)

The reaction mechanism of water splitting in natural photosynthesis

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Photosynthesis stores solar energy in chemical form, powering life on Earth, thus, inspiring technological schemes for sustainable fuel production. Today's oxygen-rich atmosphere results from photosynthetic production of O2 during the water-splitting reaction catalyzed by the oxygen evolving complex (OEC) placed in the reaction center of the Photosystem II (PSII) enzyme. The catalytic cycle leading to the water splitting into protons, electrons and molecular oxygen, consists of five consecutive steps, namely S0 – S4.
Thanks to the availability of high-resolution crystal structures since more than one decade we have investigated by classical and QM/MM simulations the catalytic mechanism of PSII and the spectroscopic properties of their intermediate states. [2-4] Recently, our study based on the combination of IR spectroscopy experiments and DFT-based calculations was able to identify the slowest step in photosynthetic O2-formation, after the S3 state and largely due to an entropic slowdown. [1]
In conjunction with previous breakthroughs in experimental and computational investigations, a compelling atomistic picture of photosynthetic O_2 formation emerges. Our results provide insights into a biological process that is likely to have occurred unchanged for the past three billion years, which we expect to support the knowledge-based design of artificial water-splitting systems.

*[1] P. Greife, M. Schönborn, M. Capone, R. Assunção, D. Narzi, L. Guidoni, H. Dau, Nature, **617**, 623 (2023)*
*[2] M. Capone, D. Narzi, D. Bovi, L. Guidoni, J. Phys. Chem. Lett., **7**, 592 (2016)*
*[3] D. Bovi, D. Narzi, L. Guidoni, Angew. Chem. Int. Ed., **52**, 11744 (2013)*
*[4] D. Narzi, D. Bovi, L. Guidoni, Proc. Natl. Acad. Sci. U.S.A., **111**, 8723 (2014)*

Topological crystal structure prediction

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The different solid structures or polymorphs of atomic and molecular crystals often possess different physical and chemical properties. Structural differences between organic molecular crystal polymorphs can affect, for example, bioavailability of active pharmaceutical formulations, the lethality of contact insecticides, and diffusive behavior in host-guest systems. In metallic crystals, structural differences may determine how different phases may be used in electronic device applications. Crystallization conditions can influence polymorph selection, making an experimentally driven hunt for polymorphs difficult. These efforts are further complicated when polymorphs initially obtained under a particular experimental protocol "disappear" in favor of another polymorph in subsequent repetitions of the experiment. Theory and computation can potentially play a vital role in mapping the landscape of crystal polymorphism. Traditional methods for predicting crystal structures and investigating solid-solid phase transformation behavior face their own challenges, and therefore, new approaches are needed. In this talk, I will show, by leveraging concepts from mathematics, specifically geometry and topology, in combination with simple physical principles, that new paradigms are emerging in our ability to predict molecular crystal structures and determine their properties.

[1] M. Tuckerman, N. Galanakis, Topological Crystal Structure Prediction (2023)

Understanding all x-ray attosecond transient absorption spectroscopy of liquid water

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There has been demonstrated success in studying ultrafast dynamics with overlapped near-infrared femtosecond and attosecond pulses combined with theory. However, true attosecond pump-probe experiments have been limited. Recently, attosecond x-ray pump/attosecond x-ray probe experiments have been realized for the first time in liquids employing synchronized pulse pairs from an x-ray free-electron laser (XFEL) (LCLS's unique $\boldsymbol{\omega}/2\boldsymbol{\omega}$ mode [1]).
In this work we demonstrate that all x-ray attosecond transient absorption spectroscopy (AX-ATAS) can resolve the electronic response of valence-ionized liquid water [2]. We have constructed a formal theory to model the pump-induced partially-coherent ionization dynamics in liquids and to interpret the AX-ATAS experimental signal. Our analysis shows that electronic hole formation through collisional ionization is ultrafast in liquid water and the AX-ATAS response is confined to the subfemtosecond timescale. That means the transient absorption signal is devoid of any effect due to nuclear motions, including the fastest moving hydrogens. Importantly, this work clearly demonstrates that the much-debated $1b_1$ splitting in the x-ray emission spectrum of liquid water is related to nuclear dynamics and is not evidence of two structural motifs in ambient liquid water.

*[1] Z. Guo, T. Driver, S. Beauvarlet, D. Cesar, J. Duris, P. Franz, O. Alexander, D. Bohler, C. Bostedt, V. Averbukh, X. Cheng, L. DiMauro, G. Doumy, R. Forbes, O. Gessner, J. Glownia, E. Isele, A. Kamalov, K. Larsen, S. Li, X. Li, M. Lin, G. McCracken, R. Obaid, J. O'Neal, R. Robles, D. Rolles, M. Ruberti, A. Rudenko, D. Slaughter, N. Sudar, E. Thierstein, D. Tuthill, K. Ueda, E. Wang, A. Wang, J. Wang, T. Weber, T. Wolf, L. Young, Z. Zhang, P. Bucksbaum, J. Marangos, M. Kling, Z. Huang, P. Walter, L. Inhester, N. Berrah, J. Cryan, A. Marinelli, Nat. Photon., **18**, 691 (2024)*

*[2] S. Li, L. Lu, S. Bhattacharyya, C. Pearce, K. Li, E. Nienhuis, G. Doumy, R. Schaller, S. Moeller, M. Lin, G. Dakovski, D. Hoffman, D. Garratt, K. Larsen, J. Koralek, C. Hampton, D. Cesar, J. Duris, Z. Zhang, N. Sudar, J. Cryan, A. Marinelli, X. Li, L. Inhester, R. Santra, L. Young, Science, **383**, 1118 (2024)*

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