BOOK OF ABSTRACT

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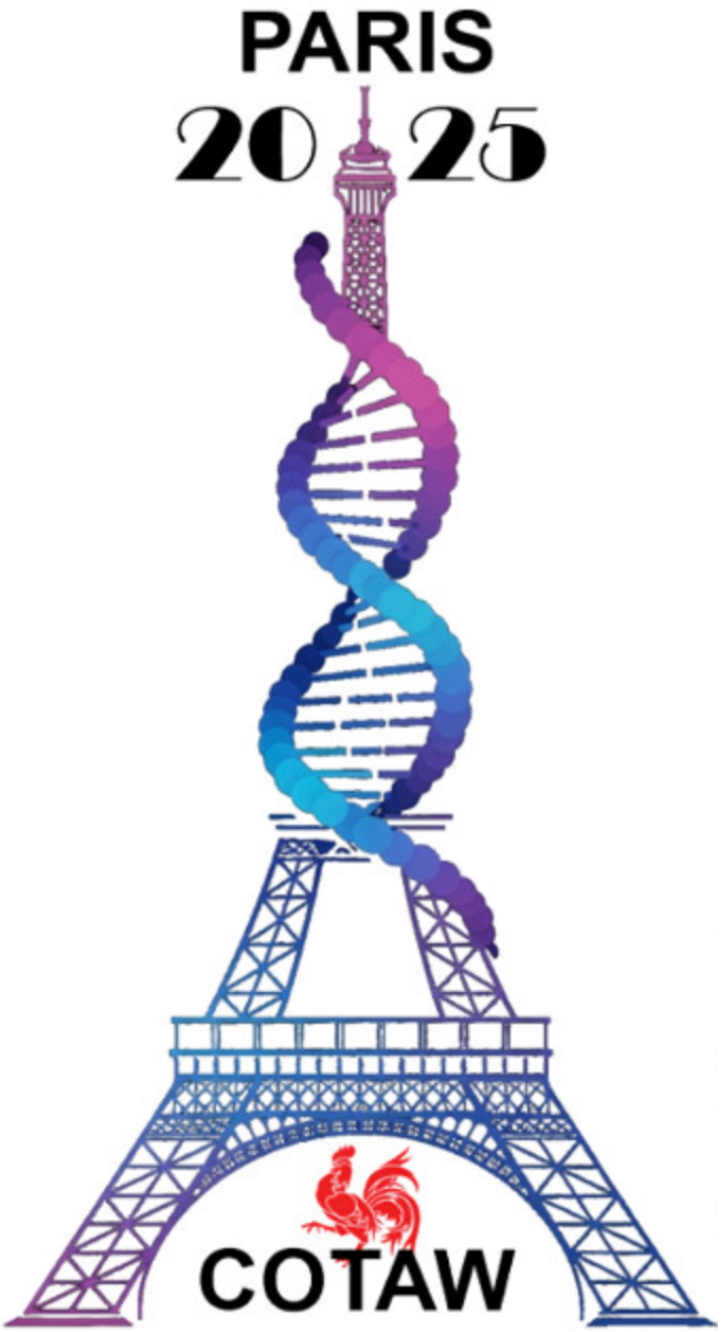

Laboratoire Itodys, room 227
15 Rue Jean Antoine de Baïf, 75013 Paris

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09:40	Abir Kebabsa	Aurianne rainot
10:00	Amina Alehyane	Emma Jung-Rodriguez
10:20	Café	Café
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Multiscale Theoretical Approaches to design Metal-Coordinated Scaffolds

Adriana Pietropaolo[1]

[1] *University of Catanzaro – Italy*

Metal-coordinated scaffolds are involved in widespread biological processes and are essential in maintaining the structural and functional complexity of natural systems.(1) More recently, inorganic frameworks garnered significant attention for biological imaging applications owing to their extraordinary emission quantum yield.(2) In this talk, I will present a suite of simulation strategies designed to investigate the dynamics,(3) metal exchange in metalloproteins,(4,5) with a particular focus on emerging workflows for studying chiral luminescent inorganic frameworks with interesting properties for imaging applications.(6-8) By integrating molecular dynamics, quantum mechanical calculations and enhanced sampling techniques, these schemes provide a robust platform for investigating coordination environments, ligand exchange processes and luminescence potential. The approach facilitates a deeper understanding of bioinspired design principles and supports the development of novel inorganic complexes that emulate the efficiency and specificity of biological systems.

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Vibrational Spectroscopy of Chromophores in Solution: a Hybrid QM/MM Dynamics Approach Enhanced by Machine Learning

Abir Kebabsa[1], François Maurel[1], Eric Brémond[1]

[1] *Laboratoire Interfaces, Traitements, Organisation et Dynamique des Systèmes (ITODYS (UMR7086)) – Université Paris cite, France*

Understanding the vibrational response of molecules in solution is crucial for various applications. However, accurately modeling vibrational spectroscopy requires a quantum mechanical treatment of the system along with a proper description of the environment. This necessity drives our investigation toward hybrid QM/MM molecular dynamics. By performing a time-series analysis of the dipole moment along a QM/MM trajectory, we model the vibrational infrared (IR) spectrum of a real-life-sized chromophore from the triangulenium family - the ADOTA carbocation - in aqueous solution. More specifically, we demonstrate that this approach is particularly well-suited for capturing the signatures of weak interactions between solute and solvent. To further enhance this analysis, we develop a machine-learning-integrated framework to identify and characterize these interactions. Additionally, we extend this work by benchmarking various quantum mechanical approaches to assess their impact on the trajectory and determine the most accurate method for predicting the vibrational signature of ADOTA

Keywords: Vibrational spectroscopy, AIMD, DFT, QMMM, Machine learning

Effects of enantiomeric excess on circular dichroism in Lead-free perovskites

Amina Alehyane[1,2] , Mariagrazia Fortino[2] , Florent Barbault[1] , Adriana Pietropaolo[2] , Antonio Monari[1]

[1] *Laboratoire Interfaces, Traitements, Organisation et Dynamique des Systèmes (ITODYS (UMR7086)) – Université Paris cite, France*

[2] *Università di Catanzaro, Italy*

Photovoltaic research is increasingly focusing on HOIPs due to their potential to surpass silicon-based panels. Additionally, their application in photoelectronic devices (OLED screens, LED switches) showing promise highlighted HOIPs as a versatile class of materials. In their class, chiral HOIPs are gaining interest due to their unique chiroptical characteristics. The introduction of chirality is done through the incorporation of chiral organic molecules into the perovskite structure, inducing asymmetry in both the crystal lattice and metal-halide coordination geometry; thereby giving rise to chiroptical effects. Despite their great potential, the relationship between the structure of chiral HOIPs and their chiroptical properties, such as circular dichroism (CD), remains incompletely understood. This project investigates the CD of a 2D chiral hybrid perovskite: (MBA)SnI, which has experimentally exhibited a prominent CD signal with excitonic splitting in the 300–500 nm wavelength range. This work focuses on 2D-layered chiral HOIPs, five models of the lead-free perovskite (MBA)2SnI4, each with a different R/S ratio of chiral MBA+ ligands, were used to investigate its CD spectrum. Our objective is to determine the specific chirality conditions that facilitate excitonic splitting in tin-based perovskites. To this end, we performed ab initio molecular dynamics (AIMD) simulations for each model using Quantum ESPRESSO software (QE) before conducting timedependent density functional theory (TD-DFT) calculations in Gaussian16 at the HSE06/LANL2DZ level on selected configurations extracted from the computed AIMD trajectories to simulate the CD spectra. By elucidating the structure-property relationships in chiral HOIPs, this study contributes to the fundamental understanding of their optical behavior and supports their development for future chiroptoelectronic applications.

Keywords: perovskites, photochemistry, TD, DFT

Exploring epigenetic mechanisms with all-atom MD simulations

Emmanuelle Bignon [1]

[1] *Laboratoire de Physique et Chimie Théoriques – Université de Lorraine, UMR7019, France*

Gene activity is tightly controlled by reversible chemical modifications called epigenetic marks, which are of various types and modulate gene accessibility without affecting the DNA sequence. Major advances come from investigations of such structural regulation at the first level of compaction of DNA, the so-called nucleosome, that is composed of ~146 base pairs of DNA wrapped around an octamer of histone proteins (1). Indeed, post-translational modifications (PTMs) of histone proteins play are major epigenetic mechanisms. For example, lysine methylation usually promotes gene silencing while acetylation are marks of gene expression. Understanding the molecular mechanisms driving such epigenetic regulation is an active field of research, and many aspects remain to be described, such as how dedicated enzymes regulate the formation and removal of histone PTMs, and how these PTMs impact the nucleosome architecture through specific structural signatures. Sirtuin 6 (SIRT6) is an NAD+-dependent histone H3 deacetylase that is prominently found associated with chromatin, attenuates transcriptionally active promoters and regulates DNA repair, metabolic homeostasis and lifespan. Unlike other sirtuins, it has low affinity to free histone tails but demonstrates strong binding to nucleosomes. It is poorly understood how SIRT6 docking on nucleosomes stimulates its histone deacetylation activity. Combining extended MD simulations to cryogenic electron microscopy (cryoEM) approaches, we revealed the structure and dynamics of the Sirtuin 6 (SIRT6) de-acetylase complexed to a nucleosome core particle (2,3). We show that in this mode of interaction, the active site of SIRT6 is perfectly poised to catalyze deacetylation of the H3 histone tail and that the partial unwrapping of the DNA allows even lysines close to the H3 core to reach the enzyme, providing new insights into the potential dynamics of SIRT6 bound to a nucleosome, that help explain its substrate specificity.

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Regulation of TIM-3 immune response through light-activated photoswitchable lipids

Anastasiia Delova[1] , Raùl Losantos [2] , Antonio Monari[1]

[1] *Laboratoire Interfaces, Traitements, Organisation et Dynamique des Systèmes (ITODYS (UMR7086)) – Université Paris cite, France*

[2] *Universidad de La Rioja, Spain*

The T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3) plays a key role in immune regulation by interacting with phosphatidylserine (PtdSer)-containing lipids. Dysregulation of TIM-3 is linked to immune tolerance, autoimmune diseases, and cancer immunotherapy. Here, we employ molecular dynamics (MD) simulations and enhanced sampling techniques to investigate the molecular mechanisms governing TIM-3 binding to lipid membranes, with a particular focus on photoswitchable lipids incorporating azobenzene and a cyclocurcumin derivative (CCBu). Our results reveal that the E/Z photoisomerization of these lipid-incorporated molecules modulates their interaction with TIM-3. The E-isomer of azobenzene-modified phosphatidylserine (PSL) exhibits strong binding affinity, stabilizing the TIM-3 immunoglobulin-like domain (IgV) and promoting receptor activation, whereas the Z-isomer leads to increased flexibility of key protein loops, weakening the binding affinity and potentially altering immune signaling. Additionally, the incorporation of CCBu into the lipid tail provides a higher level of immune response regulation. The E-CCBu conformer maintains stable interactions with TIM-3 throughout the entire simulation, while the bulkier Z-CCBu conformer fails to remain bound, suggesting that CCBu acts as an effective modulator of TIM-3 activity. Free energy calculations confirm that CCBu provides a more pronounced regulatory effect on TIM-3 activation than azobenzene derivatives, making it a promising candidate for fine-tuned immune modulation. These findings establish the molecular basis for light-induced TIM-3 modulation and highlight the potential of photoswitchable lipids and CCBu-based analogs for advanced photoimmunotherapy strategies. By leveraging E/Z isomerization, TIM-3 activity can be precisely controlled, offering new avenues for targeted immune response regulation in cancer and autoimmune diseases.

Keywords: TIM, 3, phosphatidylserine, molecular dynamics, photoswitchable lipids, cyclocurcumin, immune modulation, photoimmunotherapy.

Recognition dynamics of olfactory receptors: a molecular-scale mapping

Yani Kedjar [1]

[1] *Institut de Chimie de Nice (ICN) – Université Nice Sophia Antipolis (1965 - 2019), France*

Olfaction plays a central role in odor detection and in the modulation of eating and emotional behaviours, and its functioning can be altered by various pathologies. However, the structural complexity of olfactory receptors makes them difficult to study. This work focuses on the structural and dynamic analysis of the class II olfactory receptor ConsOR1 (PDB: 8UXY), interacting with L-menthol and several of its synthetic derivatives. Molecular dynamics simulations were used to explore the stability of the complexes formed and the flexibility of the receptor to bind odorants, as well as the conformational rearrangements of ConsOR. RMSD, RMSF and PCA analyses revealed marked differences between the ligands analysed, demonstrating the impact of size and chemical nature on receptor dynamics. Furthermore, the distances between the TM3 and TM6 helices, coupled with the free energy profiles calculated by the meta-eABF method, confirm the hypothesis of an activation mechanism dependent on the induced conformation and its interaction with given residues. These results offer a better understanding of the molecular mechanisms of olfactory receptor recognition and activation.

Keywords: Olfaction, Olfactory GPCR consensus, L, menthol, Molecular dynamics, Meta, eABF

Heavy Atom Effect For Triplet Applications With Phthalocyanines

Yilmaz Dilan [1]

[1] *Laboratoire Interfaces, Traitements, Organisation et Dynamique des Systèmes (ITODYS (UMR7086)) – Université Paris cite, France*

Heavy Atom Effect For Triplet Applications With Phthalocyanines

Impact of Ruxolitinib Interactions on JAK2 JH1 Domain Dynamics

Hong Nhung Vu [1]

[1] *Dynamics of Structures and Interactions of Biological Macromolecules (DSIMB) – Inserm – France*

Janus kinase 2 (JAK2) is an important intracellular mediator of cytokine signaling. Mutations in the JAK2 gene are associated with myeloproliferative neoplasms (MPNs) such as polycythaemia vera (PV) and essential thrombocythemia (ET), while aberrant JAK2 activity is also associated with a number of immune diseases. The acquired somatic mutation JAK2 V617F (95% of cases of PV and in 55–60% of cases of ET), which constitutively activates the JAK2, is the most common molecular event in MPN. The development of specific JAK2 inhibitors is therefore of considerable clinical importance. Ruxolitinib is a JAK inhibitor recently approved by the FDA/EMA and effective in relieving symptoms in patients with MPN. Ruxolitinib binds to the JAK2 last domain, namely JH1; its action on the dynamics of the domain is still only partially known. Using Molecular Dynamics simulations, we have analysed the JH1 domain in four different states as follows: (i) alone, (ii) with one phosphorylation, (iii) adding Ruxolitinib, and (iv) with five phosphorylations and Ruxolitinib. The ligand induces a dynamic behaviour similar to the inactive form of JH1, with a less flexible state than the phosphorylated active form of JH1. This study highlights the inhibitory effect of Ruxolitinib on the JH1 domain, demonstrating the importance of dynamics in regulating JH1 activation.

Theoretical Investigation of Bioinspired NNN-Pincer Iron Complexes for Photoelectrochemical C–H Bond Functionalization

Charles Willig [1] , Xavier Assfeld [1] , Mariachiara Pastore [1]

1 Laboratoire de Physique et Chimie Théoriques, Université de Lorraine, France

One of the holy grails of synthetic chemistry is the activation of CH bonds using cost-effective methods. Due to the high bond strength and chemical stability, CH bond activation usually requires harsh conditions, energy-intensive processes and the use of catalysts based on expensive (rare) transition metals. Our ultimate aim is to develop new catalysts based on earth-abundant metal complexes, capable of activating CH bonds using solar energy. The photoelectrochemical approach is indeed both cost-efficient and operable under mild conditions. The NNN-Pincer Iron Complexes(1) that we are studying are bioinspired by metalloenzymes like cytochrome. When oxidized, the complex catalyses the desired reaction. We will present in this lecture the preliminary steps of this study, focusing on two critical points. First, these Fe(III) complexes can exist in different spin states (high, intermediate and low spin arrangements), and it is essential to accurately describe, at DFT level, their geometries and relative energies. Second, since the photo(electro)chemical Fe(III)/Fe(IV) oxidation of the iron-pincer complex initiates the catalytic cycle, accurately predicting this redox potential considering solvent and ligand modifications is essential for guiding molecular design. To address these challenges, we performed benchmark calculations to identify the most reliable level of theory that balances accuracy and computational cost. Computed spin states and redox potentials will be presented and discussed.

Reference:
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BEYOND CONTACTS: THE IMPORTANT ROLE OF THE SUPPORT REGION TO DISTINGUISH STABLE AND TRANSIENT PROTEIN INTERFACES

Tom Miclot [1]

[1] *Laboratoire Interfaces, Traitements, Organisation et Dynamique des Systèmes (ITODYS (UMR7086)) – Université Paris cite, France*

Protein-protein interactions (PPIs) are fundamental to virtually all cellular processes; however, elucidating the principles that govern protein association into complexes remains a significant challenge. This study presents a comparative analysis of stable and transient protein interfaces, offering a detailed perspective on the interactions that form them. Moving beyond the traditional focus on pairs of neighbouring residues, the analysis examines interacting pairs by identifying their distinct non-bonded interactions. Additionally, the contextual dependence of these interactions is accounted for by analysing the regions of the interface where they occur. The approach quantifies the diversity of pairs in each region, considering the type of interface. Furthermore, an innovative strategy is introduced to analyse pair co-occurrence, enabling a comparison of the inner local organization of stable and transient interfaces. The findings reveal that stable and transient interfaces differ not in overall residue composition, but in the residue- and interaction-partitioning patterns across the variably hydrated regions of the interface. These results underscore the importance of considering the contextual environment in which pairs interact and identify the support region as a key determinant for distinguishing transient and stable protein complexes.

Functionalization of Graphene Surface to Detect Guanine Quadruplexes: an In Silico Study

Aurianne Rainot[1,2] , Florent Barbault [1] , Giampaolo Barone [2] , Alessio Terenzi [2] , Antonio Monari [1]

[1] *Laboratoire Interfaces, Traitements, Organisation et Dynamique des Systèmes (ITODYS (UMR7086)) – Université Paris cite, France*

[2] *Dipartamento Stebicef , Università degli studi di Palermo, Italy*

The quantitative detection of guanine quadruplexes (G4s) is important since they can be found in viral genomes (1) and in the promoters of oncogenes genes (2). Indeed, it would be interesting to be able to rapidly and accurately detect the presence of G4s in the context of a viral epidemic or in the context of a cancer pre-diagnosis. Thus, disposing of reliable and quantitative sensors is of outmost importance for various purposes. As a proof of concept, we propose here the modeling of a potential universal electrochemical sensor for detecting the presence of G4s. We aim to develop a device based on a Solution-Gated Graphene Transistor (SGGT), where an electrical potential is applied to the graphene electrode and the change in current is registered as a consequence of the interaction with the analyte (3,4). The surface of graphene can be functionalized to increase its sensitivity towards one particular molecule, in our case G4s. Here, the free energy profiles of the desorption of the G4s and of several molecules of interest were realized to select the best couple to ensure anchoring and selectivity. Then, we simulated the interaction with G4s of these sensitizers. As the results were satisfying, ionic density profiles were calculated to know if the functionalization of the surface and the capture of G4s were detectable.

Keywords: Biosensors, Guanine Quadruplexes, MD simulation, Umbrella Sampling

Viral RNA Recognition and Immune Activation through the OAS/RNase L Pathway

Emma Jung-Rodriguez [1] , Florent Barbault [1] , Emmanuelle Bignon [2] , Antonio Monari [2]

[1] *Laboratoire Interfaces, Traitements, Organisation et Dynamique des Systèmes (ITODYS (UMR7086)) – Université Paris cite, France*

[2] *Laboratoire de Physique et Chimie Théoriques (LPCT), Vandoeuvre-les-Nancy, France*

The activation of the OAS/RNase L pathway is a crucial component of the innate immune response against RNA viruses, initiated by the recognition of viral double-stranded RNA (dsRNA) motifs by oligoadenylate synthase 1 (OAS1) (1). This study employs a computational approach, integrating long-range molecular dynamics (MD) simulations and enhanced sampling techniques, to elucidate the molecular mechanisms governing OAS1 activation upon viral RNA binding. Through equilibrium MD simulations, we characterize the allosteric transitions between the inactive and active conformations of OAS1, demonstrating the RNA-induced structural reorganization that primes the enzyme for catalytic activity. Umbrella sampling free energy calculations reveal that RNA binding shifts the conformational equilibrium toward the active state, with an energy difference of approximately 12 kcal/mol, highlighting the role of RNA in stabilizing the active conformation. Furthermore, our analysis identifies a network of electrostatic and hydrogen bond interactions at the OAS1-RNA interface, which are crucial for recognition specificity (2). Additionally, we investigate the impact of specific RNA mutations (GC17AU and GC18AU), previously reported to downregulate OAS1 activation (3). MD simulations indicate that these mutations disrupt the hydrogen bonding network and alter the RNA-protein interface, leading to reduced enzymatic activation. These findings provide a detailed mechanistic understanding of OAS1 activation and RNA recognition, shedding light on the specificity of the immune response to viral RNA and offering insights into potential therapeutic strategies targeting the OAS/RNase L pathway.

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QM and QM/MM-MD investigations of DNA probes and photoDNAzymes: towards molecular design

Elise Dumont [1]

[1] *Institut de Chimie de Nice (ICN) – Université Nice Sophia Antipolis (1965 - 2019), Nice, France*

DNA offers a unique and inspiring playground for chemistry, yet the photophysics and photochemistry of engineered luminescent DNA probes, photoactivable G-quadruplex ligands or photocatalysts can be significantly tuned by the environment. In such contexts, one can increasingly rely on molecular modelling techniques to corroborate conformational hypothesis and generate mechanistic pathways. Molecular simulations of damaged or chemically-modified oligonucleotides or photoactivatable DNA-ligand systems enable to generate molecular structures that allow to delineate most favourable pathways. I will illustrate several tailored strategies on several systems in which classical (enhanced) MD, QM/MM(-MD) and non-adiabatic molecular dynamics simulations have been deployed to either a) unravel DNA-ligand binding modes, b) elucidate the structure and mechanism of a photoDNAzyme (3) and c) capture the active hydration role of a DNA fluorescent probe and quantify its triplet states population (2).

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Perspicacité-AI: An Open AI-Pipeline for Accelerating Scientific Education and Research

Lucas Pradi [1] , Matthieu Féraud [1] , Tao Jiang [1] , Madina Bekbergenova [1] , Louis-Felix Nothias [1]

[1] *Institut de Chimie de Nice (ICN) – CNRS, Université Côte d'Azur – France*

Science is becoming increasingly interdisciplinary, posing significant challenges for both students and researchers. We propose Perspicacité-AI, an LLM-powered agentic workflow that leverages both local and web-searched scientific literatures and provides well-researched reports with citations. This framework features advanced content retrieval methods and a novel reranking function that improves upon traditional methods by up to 3.5% across several key metrics, while addressing issues like hallucination and sourcing.

Keywords: LLM, agent, RAG

Unveiling the effect of phosphorylation on the structural and aggregation properties of DPF3a an amyloidogenic intrinsically disordered protein

Tanguy Leyder [1,2,3] , Julien Mignon [1,2,3] , Emma Bongiovanni [1] , Catherine Michaux [1,2,3]

[1] *Laboratoire de Chimie Physique des Biomolécules – Belgium*

[2] *Namur Institute of Structured Matter (NISM) – Belgium*

[3] *Namur Research Institute for Life Sciences (NARILIS) – Belgium*

The double PHD (plant homeodomain) fingers 3a (DPF3a) is a human epigenetic regulator involved in chromatin remodelling. Most notably, this protein is deregulated in various cancer types and overexpressed in neurodegenerative disorders, such as Alzheimer's and Parkinson's diseases. Recently, the disordered nature of DPF3a as well as its propensity to aggregate into amyloid fibrils have been highlighted, making it an amyloidogenic intrinsically disordered protein (IDP). Due to their high intrinsic flexibility, IDPs interact with various partners and act as hub in protein-protein interaction networks. IDPs properties are modulated by posttranslational modifications and more predominantly by phosphorylation. Indeed, such reversible modification concerns approximately a third of the eukaryotic proteome and is a modulator of IDPs function, pathogenicity, structure, and conformational state. In this context, it has already been reported that phosphorylation of Ser348 (pS348) by casein kinase 2 (CK2) is an inducer of cardiac hypertrophy through the release of transcriptional repressors HEY. Furthermore, it has been demonstrated that CK2 can also phosphorylate DPF3a at Ser138 (pS138), which is also found in an intrinsically disordered region. Nevertheless, there is currently no structural information on phosphorylated DPF3a (pDPF3a). Therefore, we use various spectroscopic, microscopic, and computational techniques to evaluate the effects of these two specific phosphorylations on the structural and aggregation properties of DPF3a. For this purpose, two

single-mutated phosphomimetics (S138E and S348E) are characterised in vitro and compared to DPF3a WT, while in silico analyses are performed on pS138 and pS348 to assess structural changes. Such investigations will help in understanding the structural features and aggregation pathways of pDPF3a for the development of specific antimitotic and anti-amyloid drugs.

Keywords: Intrinsically disordered protein, aggregation, disorder, phosphorylation, spectroscopy, microscopy, molecular dynamics

InterMap: Accelerated Detection of Interaction Fingerprints on Large-Scale Molecular Ensembles

Roy Gonzàlez-Alemàn [1]

[1] *Faculté des Sciences et Technologies (FST), Université de Lorraine, France*

Molecular dynamics (MD) simulations have become a key technique for exploring biomolecular systems at the atomic level. However, the rapid expansion of simulation capabilities has led to an increasing demand for efficient post-processing methods to derive meaningful insights from the vast amounts of data produced. Interaction fingerprints (IFPs) are a valuable tool for elucidating key atomic interactions within molecular ensembles, yet current software often struggles with extensive trajectories and complex systems. In response to this challenge, we introduce InterMap, a Python package designed to accelerate IFP detection on large-scale molecular ensembles. The package employs k-d trees to optimize distance calculations, making it especially effective in identifying intramolecular interactions. InterMap integrates seamlessly with MDAnalysis, ensuring broad format compatibility, and employs SMARTS patterns for flexible interaction definitions. Furthermore, InterMap uses efficient bit vector encoding to compress fingerprints and provides interactive visualizations that enhance data interpretation. Benchmarking results reveal that InterMap significantly surpasses available tools in processing speed (up to 1000x) and memory efficiency (up to 10x), particularly when analysing complex biomolecular systems, such as protein-DNA complexes.

Keywords: interaction fingerprints, molecular dynamics

Identification of aggregation prone regions in amyloidogenic proteins by combining multidimensional predictions and molecular dynamics

Julien Mignon [1] , Tanguy Leyder [1] , Catherine Michaux [1]

[1] *University of Namur, Chemistry Department, UCPTS – rue de Bruxelles 61, 5000 Namur, Belgium*

Alzheimer's and Parkinson's diseases occupy the leading causes of dementia and age-associated debilitating pathologies worldwide. One of their most prevalent hallmarks consists in the misfolding of proteins that subsequently self-assemble into cytotoxic aggregates (1). These highly ordered proteinaceous assemblies, referred to as amyloid oligomers and fibrils, are characterised by a cross β-sheet structure, formed by β-strands perpendicularly stacked to the fibril axis and packed into a hydrophobic steric zipper. Understanding the sequence features and identifying the regions which are the most susceptible to drive amyloid fibrillation is therefore essential for developing new strategies to target prone-to-aggregate biomolecules in proteinopathies. In such a context, we are interested in one of the isoforms of the human double PHD fingers protein 3 (DPF3a), an intrinsically disordered protein revealed to be highly amyloidogenic in vitro (2-3). Given that there is very limited structural information on DPF3a, we establish a sequence-based computational methodology, using a large array of aggregation-oriented prediction and modelling tools, to highlight amyloid hotspots. In a nutshell, we start from selecting consensus hit amyloid hexapeptides to modelling their 3D organisation into putative steric zippers that are relaxed and simulated by all-atom molecular dynamics. By submitting DPF3a sequence to the pipeline, the 52NCYIWM57 hexapeptide stood out as one of the most proamyloid stretches. Over 1 μs-triplicates, we consistently observed that 52NCYIWM57 not only retained a stable amyloid core but also was able to spontaneously self-associate into antiparallel β-sheeted oligomers upon starting from free monomers in random coil conformation. Remarkably, the relaxed steric zipper served as a templating structure, inducing monomer conversion into parallel β-strands and fibril elongation through the extension of an Asn ladder and the stacking of Tyr sidechains. Such in silico methodology holds promise for opening new avenues to disrupt

amyloidogenic proteins, especially those for which the experimental determination of their tertiary structure remains elusive.

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Investigation of protein-protein interactions in the KCTD2/17-Cullin3-Gβγ complex

Bongiovanni Emma [1], Duc Minh Nguyen[2,3], Privé Gilbert G.[2,3,4]

[1] *Laboratoire de Chimie Physique des Biomolécules, UCPTS, University of Namur, Belgium*

[2] *Princess Margaret Cancer Centre, University Health Network, Toronto, Canada*

[3] *Department of Biochemistry, University of Toronto, Toronto, Canada*

[4] *Department of Medical Biophysics University of Toronto, Toronto, Canada*

Ubiquitination is a post-translational modification that enables proteins degradation by the covalent attachment of a small protein, ubiquitin. This reaction is based on a cascade of enzymatic reactions carried out by activating (E1), conjugating (E2), and ligating (E3) enzymes. The Cullin3-RING E3 ubiquitin ligase complex (CRL3) is central to this process, relying on substrate adaptors from the KCTD protein family to ensure target specificity. Among these, KCTD5 (K5) has been previously characterized for its interactions with Cullin3 (Cul3) and G. However, despite their high sequence similarity with K5, the interaction properties of KCTD2 (K2) and KCTD17 (K17) remained poorly defined. This study aimed to quantitatively investigate the protein-protein interactions within the KCTD2/17-Cullin3-G complex. His-tagged K2 and K17 proteins were overexpressed, purified, and analysed using biolayer interferometry (BLI) to determine their binding affinities with Cul3's N-terminal domain (Cul3NTD) and G. The result demonstrates nanomolar affinities for Cul3NTD, with stronger binding observed for K17 (KD = 36 nM) compared to K2 (KD = 232 nM). In contrast, interactions with G occurend in the micromolar range, with K2 exhibiting a higher affinity (KD = 1.01 uM) than K17 (KD = 7.08 uM). These findings reveal that, despite their structural similarity, KCTD isoforms display distinct binding profiles, suggesting functional diversification in CRL3-mediated ubiquitination processes.

Keywords: Ubiquitination, protein degradation, KCTD, Cullin3, Gby, biolayer interferometry

In Silico Analysis of the Disordered Domain of the Bacterial Protein PcoB Involved in Copper Regulation

Hugo Bâlon [1] , Simon Rouxhet [1] , Jean-Yves Matroule [2] , Catherine Michaux [1]

[1] *Laboratoire de Chimie Physique des Biomolécules (CPB), UCPTS, University of Namur,Belgium*

[2] *Research Unit in Microorganisms Biology (URBM), Biology Department, University of Namur, Belgium*

The growing recognition of intrinsically disordered proteins (IDPs) in recent decades has reshaped our understanding of protein functionality, challenging the traditional structure-function paradigm by their lack of a stable three-dimensional structure. In this context, Caulobacter crescentus PcoB has been recognized as a hybrid IDP, consisting of a C-terminal β-barrel and an intrinsically disordered N-terminal domain (NTD). PcoB is a Cu(II)-efflux protein located in the C. crescentus outer membrane and is believed to function alongside the periplasmic multicopper oxidase PcoA. Together, these proteins form the Pco system, which enables bacterial survival under copper stress by mitigating its antimicrobial properties. Homologous systems are also found in pathogenic bacteria involved in nosocomial infections, such as Escherichia coli, Staphylococcus aureus or Pseudomonas aeruginosa. Due to its high conformational flexibility, PcoB is thought to function through dynamic interactions with multiple partners, including Cu(II) ions, PcoA and C. crescentus outer membrane. In this study, in silico analyses were conducted using both wild-type and point mutants of the PcoB NTD to model interaction interfaces and structural changes upon binding to metal cations, the PcoA protein, or the outer membrane. These simulations provide insights into the structural properties of the NTD and its role in the Pco-mediated copper resistance mechanism. In the long term, this research aims to gain a better overall understanding of the role of disorder in membrane proteins while providing crucial information for the development of new antibacterial strategies based on the inhibition of metal resistance systems.

Keywords: Intrinsically Disordered Proteins, Copper Resistance, PcoB, Protein–Protein Interactions, Molecular Dynamics Simulations

Structural characterisation and metal binding properties of the disordered N-terminal domain of PcoB

Simon Rouxhet[1], Hugo Bâlon[1], Andreas Prestel [2], Birthe Kragelund [2], Catherine Michaux [1]

[1] *Laboratoire de Chimie Physique des Biomolécules (CPB) – Belgium*

[2] *Structural Biology and NMR Laboratory (SBiN-Lab) – Denmark*

Intrinsically disordered proteins (IPDs) challenge the classical structure-function paradigm by exhibiting functional versatility without adopting a stable 3D conformation. The outer membrane protein PcoB from Caulobacter crescentus exemplifies this behaviour, combining a C-terminal β-barrel and a highly flexible N-terminal domain (NTD). PcoB is a Cu(II)-efflux protein involved in the Pco copper regulation system. Due to its conformational flexibility, PcoB NTD is likely engaged in dynamic interactions with multiple partners, including Cu(II) ions, potentially driven by its high histidine (His) content. This study focuses on the structural and functional characterisation of PcoB NTD. Circular dichroism and nuclear magnetic resonance (NMR) spectroscopy were used to confirm its intrinsically disordered nature, while also revealing the presence of helical regions near the β-barrel. Its interactions with Cu(II) ions, as well as with other divalent cations to evaluate the selectivity, were explored through intrinsic tyrosine fluorescence, isothermal titration calorimetry, and NMR spectroscopy. These techniques revealed micromolar affinities for Cu(II) ions, as well as for Zn(II), Ni(II) and Co(II) ions, with interactions showing strong pH dependence and involving His residues. Future studies using PcoB NTD mutants could help confirm the specific contribution of these histidines to metal coordination. Altogether, our data provide new insights into the structural plasticity and metal binding capacity of PcoB NTD, supporting its role as a flexible interface in copper detoxification.

Keywords: PcoB, IDR, Membrane protein, Metal binding

Dynamical resolution of Near-UV circular dichroism spectra of protein

Jeremy Morere [1]

[1] *Laboratoire de Physique et Chimie Théoriques (LPCT), Université de Lorraine, Vandoeuvre-les-Nancy, France*

Circular dichroism (CD) measures the difference in absorption of left and right circularly polarized light. Near-UV CD spectroscopy is a sensitive tool to explore the tertiary structure of biomolecules such as proteins, DNA, or RNA. As proteins are systems of up to several thousand atoms, it is not possible to perform a single calculation at the quantum level to obtain the desired spectrum. Numerous methods have been developed to solve this problem. The matrix method was introduced to overcome this problem in the general case of large systems. This method involves separating the system into several photoactive groups, each of which is treated separately for quantum calculation. The interactions between the groups are introduced using an effective Hamiltonian involving individual electric and magnetic properties. Existing software allows spectra to be calculated, but there are several limitations. Most of the programs available concentrate on the middle-UV and far-UV regions. In addition, the matrix method, when used, prefers to use a parameterization of the photoactive groups. Proteins can adopt a wide variety of conformations, and all contribute to the CD experimental near-UV CD spectra. Thus, theoretical predictions of near-UV CD spectra that relied on a single static conformation can fail to capture this dynamical effect. We propose an approach for calculating near-UV CD spectra without parametrization in order to take into account the environment of each photoactive group. Indeed, their environment changes between different proteins and within the same protein depending on its conformation. The approach is based on the matrix method, where all individual properties used will be calculated using quantum mechanics/molecular mechanics (QM/MM). The space of all conformations taken by the protein is sampled with molecular dynamics (MD). For each snapshot, the spectrum of the associated conformation is calculated. The spectrum with the dynamic effects is obtained by averaging all the spectra obtained. This methodology has been fully automated in DichroProt, an open-source pipeline capable of processing MD trajectories, performing QM/MM calculations, and generating ensemble-averaged CD spectra