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Welcome

Dear colleagues and friends,

It is with great pleasure that we, the members of the GGMM board, the organizing and the scientific committees, extend a cordial welcome to you all at GGMM2025 in Forges-les-Eaux. The organising committee has selected a peaceful environment, allowing for convivial and friendly exchanges before, during and after the conferences, poster exhibitions and software demonstrations. It is evident that the 24th biennial GGMM Congress is already proving to be an unprecedented success, with a participants number of 129 in global, being reached in a record time. The scientific program, meticulously organised by the event's planners, is no stranger to success. In this regard, we would like to extend our gratitude to the speakers who graciously accepted our invitation: Giorgia Brancolini from Modena (Italy), Barbora Kozlikova from Brno (Czech Republic), Aurélien De La Lande from Paris Saclay University, Jessica Andréani from CEA and Massimiliano Bonomi from the Pasteur Institute. We also thank our young invited speakers: Paulo de Souza, Vaitéa Opuu, Nathalie Lagarde, Claire de March, and Natacha Gillet. The programme will feature over 29 short oral communications and 54 posters, which will enrich the various sessions devoted to interface modelling, artificial intelligence applied to structural bioinformatics, multi-scale simulations, visualisation and graphics, drug design and integrative modelling. As is the case every 2 years, there will be an interlude to allow the general assembly to take place. The scientific committee will determine the most outstanding poster and oral communication, and prizes will be awarded to the respective winners. Ultimately, I will have the privilege of presenting the GGMM thesis prize to Mariia Avstrikova, who has been selected by the members of the GGMM board for her original and impactful work. We would like to express our gratitude to all the sponsors who have made it possible to organise this congress in the best possible conditions, and hope that you will have a fruitful time strengthening your ties and forging new ones within this growing, dynamic and caring community!

Welcome to Normandy !

Nicolas Renault, president of the GGMM association

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Program

Tuesday, 10th June 2025

14:00-14:15 Welcome speech

Interface modelling

14:15-15:00 **Keynote 1**: *In Silico Strategies for Biofunctionalized Interfaces: Modeling Molecular Interactions at the Nanoscale* : Giorgia Brancolini

15:00-15:15 *Coarse-grained molecular dynamics simulation of liquid-liquid phase separation of intrinsically disordered proteins* - Yingmin Jiang, Université Paris Saclay

15:15-15:30 *Creation of stable biomimetic nanopores in view of water sea desalination* - Fatouma Hassan Moussa, SINERGIES (Soins intégrés, Nanomédecine, IA, Ingénierie pour la Santé)

15:30-15:45 *Deciphering DFR substrate specificity and metabolic interactions using molecular dynamics and amino acid network analysis* - Lucas David, Institut de Chimie de Nice, Université Côte d'Azur

15:45-16:05 *Invited 1: Enhancing Coarse-Grained Models for Lipid Nanoparticle Design and Optimization* - Paulo C. T. Souza, Laboratoire de Biologie et Modélisation de la Cellule, Lyon, France.

16:05-16:15 Flash Poster session 1: P1 to P12

16:15-16:45 Coffee break

16:45-17:00 *In Silico Study: Functionalization of a Graphene Surface for Detection of Guanine Quadruplexes* - Aurianne Rainot, Interfaces, Traitements, Organisation et Dynamique des Systèmes, Dipartamento Stebicef, Università degli studi di Palermo

17:00-17:15 *New players and metrics in challenging interfaces: the multiphosphorylated Tau-R2/tubulins complex as a case study for fuzzy interactions* - Jules Marien, Laboratoire de biochimie théorique

17:15-17:30 *In Design and Prediction of Structural Properties of Dimerization Interfaces of Drosophila Melanogaster Gluthatione Transferases* - Nicolas Petiot, Laboratoire Interdisciplinaire Carnot de Bourgogne

Structural Bioinformatics and AI

17:30-18:15 **Keynote 2**: *Deciphering macromolecular interactions through AI-powered structural modeling and evolutionary perspectives*: Jessica Andréani, Institute for Integrative Biology of the Cell (I2BC), CEA Paris-Saclay University

18:15-18:30 *A Generative Hybrid Artificial Intelligence Approach for Designing Protein Assemblies* - Delphine Dessaux, Toulouse Biotechnology Institute

18:30-18:45 *Leveraging computational methods for protein engineering* - Jelena Vucinic, Schrödinger

18:45-20:30 **Poster session**

20:30-22:00 Dinner

Wednesday, 11th June 2025

08:30-08:50 Invited 2: *Bridging machine learning and biophysics to expand RNA functional diversity* - Vaitéa Opuu, ESPCI

08:50-09:00 Flash Poster session 2: P13 to P24

09:00-9:15 *Advanced molecular dynamics simulations and AI for investigating and modulating ABC transporters* - Ahmad Elbahnsi, Inserm U1268 MCTR, CiTCoM CNRS, Université Paris Cité

9:15 - 9:30 *A Single Framework to Accurately Predict Multiple Impact of Genetic Variants*- Ragousandirane Radjasandirane, Université Paris Cité, BIGR

9:30-9:45 *Molecular modelling of an intrinsically disordered protein (IDP), human endosulfatase 2 (HSULF2)* -Jianjun Tao, LAMBE, Université d'Evry-Val d'Essonne

9:45-10:00 *Study of the Interaction Between MSMP and CCR2 Proteins using molecular dynamic simulations and machine learning* - Léopold Quitté, GHU AP-HP Nord, Université Paris Cité, Centre Hospitalier Université Laval, Canada

10:00-10:30 Coffee break

Visualization, Graphism and Drug Design

10:30-11:15 **Keynote 3**: *Design of Visualization Support for Molecular Visualization* - Barbora Kozlikova, Faculty of Informatics, Masaryk University, Brno, Czech Republic Barbora Kozlikova

11:15-11:30 *In sillico studies of a membrane transporter involved in antibiotic resensitization* - Côme Ghadi, UR 4258 CERMN, Centre d'Etudes et de Recherche sur le Médicament de Normandie

11:30-11:45 *UnityMol-Lite: Cross-platform Collaboration and Interactive Methods for Molecular Modeling in Extended Reality* - Mariano Spivak, Virtual & augmented ENvIronments for Simulation & Experiments - LISN, Laboratoire de Biochimie Théorique - Institut de Biologie Physico-Chimique

11:45-12:00 *Unveiling G-Protein-Coupled Receptor Conformational Dynamics via Metadynamics Simulations and Markov State Models* Rita Ann Roessner, University of Montpellier

12:00-12:20 Invited 3: *Targeting IL-4/IL-13 Protein-Protein Interactions to Develop Small-Molecule Therapies for Asthma*- Nathalie Lagarde, CNAM, Paris

12:20-12:30 Flash poster session 3: P25-P42

12:30-14:00 Lunch

14:00-14:15 *ComPASS, an efficient method to reveal communication pathways within protein-nucleic acid complexes*- Yasaman Karami, Laboratoire Lorrain de Recherche en Informatique et ses Applications

14:15-14:30 *Designing of novel broad spectrum antivirals* - Marc Farag, Institut de Chimie Organique et Analytique, Université d'Orléans, CNRS

14:30-14:45 *TNFα:TNFR1 complex in a membrane context: structural and functional insights* - Elena Álvarez Sánchez, Unité en Sciences Biologiques et Biotechnologies de Nantes

14:45-15:00 *Efficient compound selection strategies in lead optimization: insights from retrospective analysis* - Pablo Mas, Laboratory CPCV, Sanofi-aventis recherche et développement, Integrated Drug Discovery, Molecular Design Sciences

Integrative Modeling

15:00-15:45 **Keynote 4**: *Structural and dynamic biology with integrative approaches*- Massimiliano Bonomi, 1Institut Pasteur, Université Paris Cité, CNRS UMR 3528

15:45-16:00 *Auto-Martini Update for Martini 3: Still Fast and Furious, Now More Accurate and Versatile* - Magdalena Szczuka, Centre de Biologie Intégrative, Université de Toulouse, Eurofins Calixar

16:00-16:30 Coffee break

16:30-16:45 *Bayesian Analysis of Constant pH MD and Protonation Couplings* - Eliane Briand, Max Planck Institute for Multidisciplinary Sciences

16:45-17:00 *HADDOCK3, a modular platform for biomolecular integrative modelling* - Raphaëlle Versini, Utrecht University

17:00-17:20 Invited 4: *Structural elucidation and molecular mechanisms of mammalian odorant receptors* - Claire de March, Institute of Chemistry of Natural Substances, CNRS Paris Saclay University

17:20-17:30 Flash poster session 3: P43-P54

17:30-17:45 *Water Molecules as Molecular Probes: Understanding and Reshaping Enzyme Interiors* - Gamze Tanriver, Tunneling Group, Biotechnology Centre, Silesian University of Technology

17:45-18:00 *Unraveling the Impact of Cofactors on the Dynamics of BVMO enzymes.* - Joseph Rebehmed, Department of Computer Science and Mathematics, Lebanese American University

18:00-18:15 *Kinetics rates calculations of β2-adrenergic receptor-ligand assemblie* - Romain Launay, BioCIS - Université Paris-Saclay - CNRS UMR 8076

18:15-18:30 *Structure resolution of glucose units in a heparan sulfate mimetic (RGTA®) fragment by NMR and molecular dynamics simulations* - Aubert De Lichy, Organ, Tissue, Regeneration, Repair, Replacement (OTR3), Université Paris Est Créteil (UPEC), Glycobiology, Cell Growth and Tissue Repair Research Unit (Gly-CRRET)

18:30-18:45 **GGMM General Assembly**

18:45-20:30 **Poster Session 2**

20:30-24:00 Gala Dinner

Thursday, 12th June 2025

Multi-scale calculations

8:30 - 9:15 **Keynote 5** *Computer Modelling of Electron Transfers in Complex Biological Structures* - Aurélien De La Lande, Institut de Chimie Physique, Université Paris Saclay, CNRS (UMR 8000), Orsay, France

9:15-9:30 *Histidine 73 methylation coordinates β-actin plasticity in response to key environmental factors* - Adrien Schahl, Université Sorbonne Paris Cité, Institut de pharmacologie et de biologie structurale, KTH Royal Institute of Technology, Stockholm

9:30-9:45 *Investigating SHAPE chemical reactivity of RNA molecules using a multiscale approach* - Ameni Ben Abdeljaoued, Université Paris Cité, CiTCoM, CNRS

9:45-10:00 *Sampling Effects on Photophysical Properties of Biliverdin in the GAF Domain of Bacterial Phytochrome by Advanced Molecular Dynamics Simulations* - Volkan Findik, Université Gustave Eiffel

10:00-10:30 Coffee break

10:30-10:50 Invited 5: *Multi-scale molecular dynamics simulations for oxidative damages in nucleosomal DNA: from ionization to repair* - Natacha Gillet, ENS de Lyon, CNRS, LCH, UMR 5182

10:50-11:05 *Multiscale in silico modeling and simulation of an antibody at ultra-low temperatures: impact of cryoprotectants and insights into the dimerization phenomenon.* - Ravy Leon Foun Lin, Department of Biological Research on the Red Blood Cells, Université Paris Cité and Université des Antilles and Université de la Réunion, INSERM, BIGR, DSIMB Bioinformatics Team, F-75014 Paris, France, Audensiel Healthcare

11:05-11:20 *Vibrational Spectroscopy of Chromophores in Solution: a Hybrid QM/MM Dynamics Approach Enhanced by Machine Learning* - Abir Kebabsa, Interfaces, Traitements, Organisation et Dynamique des Systèmes

11:20-11:35 *Computational prediction of modulatory ligands binding in synaptic receptors* - Hryhory Sinenka, Laboratoire d'Ingénierie des Fonctions Moléculaires

11:35-11:55 **GGMM Thesis Prize**: Mariia Avstrikova - *Exploring the Allosteric Modulation of the Nicotinic Acetylcholine Receptor α7 by Molecular Dynamics Simulations*

11:55-12:05 **Poster and oral prizes - Closing ceremony**

Keynote speakers

Session 1: Interfaces modelling

-Keynote Speaker: Dr. Giorgia Brancolini, CNR Senior Researcher, Institute of Nanosciences, Modena, Italy

The booming field of interface modeling is now essential for studying the behavior of biomolecules in interaction with nanoparticles, inorganic surfaces, or even plastic polymers. Numerous applications, such as the study of the toxicity of nanomaterials, the fight against nosocomial infections, the design of biosensors, and the degradation of plastics, illustrate the growing importance of this approach, especially in a context where experimental data are unfortunately rare. To give the plenary conference on this topic, we invited Dr. Giorgia Brancolini, a researcher at the Institute of Nanosciences in Modena, Italy. Dr. Brancolini has been exploring solid interface modeling for more than ten years and is recognized as an authority in this field.

Session 2: Structural Bioinformatics and AI

-Keynote Speaker: Dr. Jessica Andréani, I2BC, Research director at CEA

This session will focus on the use and development of AI in molecular modeling. This field was honored with the 2024 Nobel Prize in Chemistry. It has significantly expanded our knowledge in structural biology, chemistry, and biophysics. As our keynote speaker, we are pleased to welcome Dr. Jessica Andréani, a research director at CEA, who has conducted groundbreaking studies on macromolecular structure prediction using AI.

Session 3: Visualization, Graphism and Drug Design

-Keynote Speaker: Dr. Barbora Kozlíková, Masaryk university, Brno, Cszech Republic

This theme is transversal in nature and requires numerous technical and methodological developments. In order to represent this subject, we contacted Ms. Barbora Kozlíková, from the Faculty of Informatics at Masaryk University, in the Czech Republic. Ms. Kozlíková is widely recognized in the field of molecular graphics, particularly for her contributions to the development of software dedicated to the visualization and analysis of interactions between a ligand and a protein.

Session 4: Integrative modeling

-Keynote Speaker: Dr. Massimiliano Bonomi, CNRS Research Director, Pasteur Institute, Paris

This approach enables the integration of various experimental and theoretical data to develop more comprehensive and precise models of complex biological systems, such as proteins, macromolecular complexes, or even cellular interaction networks. To address this subject, we invited Dr. Max Bonomi from the Institut Pasteur, an eminent figure in the field of integrative molecular modeling.

Session 5: Multi-scale calculations

-Keynote Speaker: Dr. Aurélien de La Lande, CNRS Research Director, Université Paris-Saclay

Structural biology, situated at the intersection of biological complexity, brings together the immensity of biological polymers with the precision of the atomic scale. The pursuit of greater precision through hybrid methods, such as QM/MM, enables the analysis of phenomena like reactivity, oxidation states, and the spectroscopic properties of biomolecules. To address this topic, we invited Dr. Aurélien de La Lande, research director at the CNRS in Orsay, who is renowned in the field of QM/MM and can offer valuable insights and a critical perspective on the limitations of these approaches.

10th June 2025

Session 1: Integrative modeling

14:15-17:30

Keynote Speaker: Giorgia Brancolini

Invited Speaker: Paulo C. T. Souza

Keynote 1: In Silico Strategies for Biofunctionalized Interfaces: Modeling Molecular Interactions at the Nanoscale

Giorgia Brancolini * [1]

[1] Institute Nanoscience – CNR-NANO, Center S3, via G. Campi 213/A, 41125, Modena, Italy

In silico modeling is a powerful tool for understanding biomolecular interactions with solid interfaces, advancing biosensing, diagnostics, and therapeutics. In this keynote, I will present a multiscale computational protocol to enhance biosensor design for West Nile Virus (WNV) detection. By comparing gold nanoclusters and flat surfaces, we identify optimal DNA aptamer anchoring strategies and evaluate the impact of physiological conditions on sensor stability. Additionally, I will discuss a multiscale approach for reversible IL-6 detection in cancer biosensors and the interaction of phosphorene nanoparticles functionalized with curcumin for photothermal and photodynamic antibacterial therapies. This integrated framework provides insights into biointerface engineering, with broad applications in infectious disease detection and nanomedicine.

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[2] M. Weigt, R. A. White, H. Szurmant, J. A. Hoch, and T. Hwa. Identification of direct residue contacts in protein-protein interaction by message passing. Proceedings of the National Academy of Sciences, 106(1):67–72, 2009.

*Speaker

Coarse-grained molecular dynamics simulation of liquid-liquid phase separation of intrinsically disordered proteins

Yingmin Jiang * [1], Tâp Ha-Duong [1]

[1] Université Paris Saclay – BioCIS – France

Liquid-Liquid Phase Separation (LLPS) is a spontaneous process in which molecules within a solution undergo phase separation, leading to the formation of distinct liquid phases and the emergence of droplets or condensates. These phenomena are particularly noteworthy in eukaryotic cells, where certain condensates, devoid of a lipid membrane and termed membraneless organelles (MLOs), play diverse roles. Notable examples include nucleoli, Stress granules, P-bodies and so on (1,2).
Intrinsically Disordered Proteins (IDPs), with their highly dynamic structures and the ability to facilitate multivalent interactions, are closely associated with phase transitions and condensate formation (3). However, the intricate interplay of intramolecular and intermolecular interactions can be modulated by environmental factors such as temperature, specific small molecules or salts concentrations, and pH.

Thermoresponsive IDP-based polymers, exhibiting reversible changes in solubility based on temperature, provide a promising avenue to address certain disease challenges. The temperature-transferable Coarse-Grained (CG) model, specifically optimized in this study, proves effective in reproducing both Upper Critical Solution Temperature (UCST) and Lower Critical Solution Temperature (LCST) behaviors of IDP LLPS (4).

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(4) Best R B. Computational and theoretical advances in studies of intrinsically disordered proteins(J). Current opinion in structural biology, 2017, 42: 147-154.

*Speaker

Creation of stable biomimetic nanopores in view of water sea desalination

Fatouma Hassan Moussa * [1]

[1] SINERGIES (Soins intégrés, Nanomédecine, IA & Ingénierie pour la Santé) – Université Marie et Louis Pasteur, CNRS, institut FEMTO-ST, F-25200 Montbéliard, France – France

One of the major challenges of the 21st century is access to clean water. Its availability is expected to decrease in the coming years due to climate change, population growth, and pollution, leading us towards a potential shortage of potable water. Current water desalination technologies are limited due to their high costs and high energy consumption. Hence the urgent needs for sustainable solutions. Scientific research is beginning to explore ways of developing bio-inspired functional materials for water filtration and purification processes. In this work, we envisage the creation of artificial ion channels mimicking natural biological channels using high performance simulations. For this, we use a synthetic material (i.e. carbon nanotubes) to minimize energy consumption in a desalination system, coupled with a transmembrane polypeptide called gramicidin A (gA). Cautions have been taken to transfer proteins into artificial nanopores, as the environment differs from that of lipid membranes. We will present here the different phases of optimization of this novel biomimetic nanofluidic system, from the best carbon nanotube geometry to stabilize the polypeptide to the best conditions of voltage (from static to periodic) to discriminate ions through the channel and desalinate water at best.

*Speaker

Deciphering DFR substrate specificity and metabolic interactions using molecular dynamics and amino acid network analysis

Lucas David* [1] Serge Antonczak [1] Christian Haselmaier-Gosch [2] Heidi Halbwirth [2]

[1] Institut de Chimie de Nice, Université Côte d'Azur
[2] Institute of Chemical, Environmental and Bioscience Engineering, TU Vienna, Austria

Among the diverse metabolites synthesized by plants, polyphenols represent one of the most abundant families, with anthocyanins playing a central role in determining plant petals color. The dihydroflavonol 4-reductase (DFR) is a key enzyme in flavonoïd biosynthesis, catalyzing the reduction of dihydroflavonols (DHK, DHQ or DHM) into leucoanthocyanidins. While some DFRs exhibit low substrate specificity, others are highly selective, leading to species-specific color variations (1). Although substrate preference has been shown to be linked to the presence of specific amino acids in the catalytic site (2), a complete understanding of substrate specificity requires investigating a wider interaction network within the enzyme. To gain deeper insights into DFR specificity, we carried out several long molecular dynamics (MD) and QM-MM/MD simulations (AMBER). Beyond focusing on single amino acid changes in the active site, we also analyzed correlated interactions within the enzyme using protein network based approaches (PSNtools, Sensenet ...). This allowed us to confirm and complete a list of key residues involved in direct substrate stabilization but also to characterize a set of second-layer amino acids preventing these to lose their stabilization. Comparing the networks produced from the DFR-bound and unbound states of our ligands offers interesting insights into explaining the substrate recognition pattern underlying the specificity of our enzyme. Other factors may impact this enzyme specificity, such as allosteric modulation by protein-protein interaction and high metabolite concentrations. We thus perform long MD simulations of DFR interacting with ANS (Anthocyanidin synthase), the next enzyme in the biosynthetic pathway, but also surrounded by many polyphenol type compounds. Forthcoming network analysis should then reveal the impact of these factors on the specificity of DFR enzyme. This work sheds new light on the determinants of DFR specificity and paves the way for a better understanding of enzymatic selectivity in plant secondary metabolism.

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(1) Christian Haselmair-Gosch et al., " Great Cause-Small Effect: Undeclared Genetically Engineered Orange Petunias Harbor an Inefficient Dihydroflavonol 4-Reductase ", Frontiers in Plant Science vol 9 (2018)

(2) Julien Diharce et al., " Exploring Dihydroflavonol-4-Reductase Reactivity and Selectivity by QM/MM-MD Simulations ", Chembiochem: A European Journal of Chemical Biology vol 23 (2022)

*Speaker

Invited 1: Enhancing Coarse-Grained Models for Lipid Nanoparticle Design and Optimization

Paulo C. T. Souza* [1] [2]

[1] Laboratoire de Biologie et Modélisation de la Cellule, CNRS, UMR 5239, Inserm, U1293, Université Claude Bernard Lyon 1, Ecole Normale Supérieure de Lyon, 46 Allée d'Italie, 69364, Lyon, France.
[2] Centre Blaise Pascal de Simulation et de Modélisation Numérique, Ecole Normale Supérieure de Lyon, 46 Allée d'Italie, 69364, Lyon, France.

Lipid nanoparticles (LNPs) are a versatile and highly effective platform for drug and nucleic acid delivery. However, optimizing their composition for specific cargos and cellular targets remains a complex challenge, requiring a deeper understanding of their structural and physicochemical properties. Experimental methods, while valuable, are costly and often provide low-resolution data. Molecular dynamics (MD) simulations enable high-resolution studies, but atomistic simulations are computationally expensive and time-consuming (1,2). Coarse-grained (CG) models, such as Martini 3 (3), offer a promising alternative for studying LNPs efficiently1,2. To support CG-MD investigations, accurate and validated LNP component models are essential. In this work, we enhance the Martini 3 lipid library by refining the resolution and thermodynamics of lipid tails (4) and introducing hundreds of ionizable lipid (IL) models, along with naturally occurring sterols and PEGylated lipids—key components of LNP formulations5. Additionally, we propose initial protocols for evaluating fusion efficiency across lipid formulations and constructing complete LNPs at a CG resolution (5). Furthermore, we explore the integration of CG simulations with machine learning techniques to enable accelerated screening and optimization, paving the way for more efficient and data-driven LNP design in drug and nucleic acid delivery.

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*Speaker

In Silico Study: Functionalization of a Graphene Surface for Detection of Guanine Quadruplexes

Aurianne Rainot* [1] [2] Florent Barbault [1] Giampaolo Barone [2] Alessio Terenzi [2] Benoit Piro [1] Antonio Monari [1]

[1] Interfaces, Traitements, Organisation et Dynamique des Systèmes, CNRS, Université Paris Cité
[2] Dipartamento Stebicef, Università degli Studi di Palermo, Italy

The ability to quantitatively detect guanine quadruplexes (G4s) is important, as they are present in viral genomes (1) and in the promoters of oncogenes (2). Quickly and accurately identifying G4s would be beneficial during a viral epidemic or in the context of cancer pre-diagnosis. Thus, disposing of reliable and quantitative sensors is of outmost importance for various purposes. In this proof of concept, we present an in silico model for a potential universal electrochemical sensor designed to detect 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, thanks to classical and enhanced molecular dynamic simulations we assess a couple of molecule to ensure anchoring to the surface and selectivity towards G4s as a bifunctional molecule or sensitizer. We then simulated the interaction of these sensitizers with G4s. The results were promising, and ionic density profiles were calculated to assess the detectability of G4 capture after surface functionalization.

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*Speaker

New players and metrics in challenging interfaces: the multiphosphorylated Tau-R2/tubulins complex as a case study for fuzzy interactions

Jules Marien* [1] Chantal Prevost [1] Sophie Sacquin-Mora [1]

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Fuzzy complexes involving Intrinsically Disorded Regions and Proteins (IDRs and IDPs) have emerged as a new frontier in our understanding of protein-protein interactions in the latest years. The ability of one or more constituents of a complex to remain disordered challenges our usual assumptions, analysis techniques and metrics (1). Interactions between disordered tubulin C-Terminal Tails (CTTs) and R2, in addition to recently characterized nP-collabs (2), make the phosphorylated Tau-Microtubule complex a valuable case study for the characterization of fuzzy interfaces with post-translational modifications (3). We performed all-atom molecular dynamics simulations on a trimeric tubulin complex bound to the R2 repeat domain of the Tau protein, and studied the effects of the different phosphorylation states of R2 (4). We provide evidence for a new stabilizing interface mechanism of the CTTs around R2 termed "wrapping phenomenon", and discuss the different binding interactions of R2 to the tubulin cores. The role of bulk ions in inter-molecular nP-collabs will be emphasized as an agent of (over?)stabilization of the complex. We also present 3 new metrics (the Proteic Menger Curvatures, the Local Curvatures and the Local Flexibilities) to study IDRs, IDPs and fuzzy complexes (2).

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*Speaker

In Design and Prediction of Structural Properties of Dimerization Interfaces of Drosophila Melanogaster Gluthatione Transferases

Nicolas Petiot* [1] Mathieu Schwartz [2] Patrice Delarue [1] Patrick Senet [1]
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Glutathione Transferase (GST) is a superfamily of ubiquitous enzymes, multigenic in several organisms. Typically, GSTs function as homodimers, where the dimerization interface plays a crucial role in maintaining structural stability and catalytic activity (1). The primary biological role of GSTs is to catalyze the conjugation of reduced glutathione (GSH), their cofactor, to hydrophobic xenobiotic centers. Each GST subunit contains two distinct binding sites: a highly conserved Glutathione-binding site (G-site) and a more variable ligand-binding site (H-site), which accommodates diverse substrates.
In this study, we focus on the model organism *Drosophila melanogaster* (fruit fly, *D. mel*), which comprises 42 GST sequences grouped into six classes, collectively known as its GSTome. Through a comprehensive structural analysis of the *D. mel* GSTome (2), we identified key residues and motifs critical for the dimerization process and structural stability of GSTs. Additionally, based on the sequence conservation within the *D. mel* GSTome, we performed Monte Carlo Sampling in Sequence Space (MCSS) to optimize the dimerization interfaces of GST enzymes. Single-mutation structures were predicted using AlphaFold2-multimer. Optimized sequences and structures were evaluated and ranked according to energy minimization in vacuum.

From sequence distributions, we identified new dimerization motifs along with their corresponding structural designs, comparing them to known GST dimerization motifs such as Wafer and Clasp. Finally, we validated the stability and dimerization energies of the designs using classical all-atom Molecular Dynamics simulations in explicit solvent. We then constructed free energy landscapes using both coarse-grained and side-chain dihedral angle internal coordinates. This approach allowed us to correlate local conformations in the dimerization interfaces with interaction energies between subunits.

As a next step, GST designs will be synthesized and experimentally validated through *in vitro* testing to confirm the impact of sequence modifications on stability. This methodology will also be extended to investigate protein-ligand interactions within GSTs.

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*Speaker

10th June 2025

Session 2: Structural Bioinformatics and AI

17:30-18:45

Keynote Speaker: Jessica Andréani

Deciphering macromolecular interactions through AI-powered structural modeling and evolutionary perspectives

Jessica Andréani * [1]

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Interactions between macromolecules, including proteins and nucleic acids, play a central role in many biological processes, and their disruption often has pathological consequences. Precise knowledge of the 3D structure provides invaluable insight into understanding and modulating these assemblies. The challenges inherent to experimental structure determination have motivated the development of numerous computational prediction methods over the last fifty years, and the most recent approaches, powered by artificial intelligence, have achieved unprecedented success.
I will present a brief overview of methodological approaches to protein complex structure prediction, including past contributions to the improvement of protein-protein docking using evolutionary information, and recent developments relying increasingly on AI-based strategies, such as AlphaFold. I will illustrate the opportunities that these recent approaches offer for the structural prediction of macromolecular complexes. I will also describe how we analyzed structural data to investigate how selection pressures affect the evolution of protein-RNA interfaces, and I will give some perspectives on how to connect this study with remaining challenges and upcoming research regarding the structural prediction of protein-nucleic acid interfaces.

*Speaker

A Generative Hybrid Artificial Intelligence Approach for Designing Protein Assemblies

Delphine Dessaux* [1] Marianne Defresne [1 2] Samuel Buchet [2] Lucie Barthe [1] Liza Ammar Khodja [3] Simon De Givry [2] Gianluca Cioci [1] Luis Garcia-Alles [1] Alain Rousell [3] Thomas Schiex [2] Sophie Barbe [1]

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Protein-protein interactions (PPIs) are fundamental to biological system functions, governing a wide range of cellular processes. Thus, the design of protein assemblies enables the construction of novel biomolecular structures with tailored functionalities, contributing to advancements in synthetic biology, nanotechnology, and biomedicine. When designing or modifying protein interfaces, most classical computational protein design (CPD) approaches generally consider only a single, rigid state representing the interaction between partners, preventing the consideration of specificity and flexibility requirements inherent in most protein complexes. While the recent development of artificial intelligence (AI)-powered algorithms is extending the possibilities of protein interface design by better addressing the dynamic nature of protein interactions, common autoregressive models such as ProteinMPNN have their limitations. Indeed, these methods sequentially generate protein sequences, predicting amino acids one by one, and hence are hindered by their prior choices.

To overcome these limitations, we developed an AI approach that merges deep learning with automated reasoning, two areas of artificial intelligence. This novel approach integrates a deep-learned pairwise decomposable scoring function called Effie, with an advanced reasoning method for multicriteria optimization, enabling the incorporation of a large range of constraints, including symmetry, composition, and the consideration of multiple states representative of protein flexibility. Moreover, this approach can be applied to negative design problems, explicitly considering both positive and negative states to favor desired interactions over undesired ones, thereby ensuring interaction specificity. We demonstrated the versatility of this framework through two key applications.

First, our hybrid-AI approach was employed to design RMM, a hexameric protein component of the shell of bacterial microcompartments (BMC), to predict sequence pairs, A and B, that can preferentially self-assemble in heterohexamers ABABAB over homohexamers. Eventually, interaction between a few of designed AB proteins was experimentally verified using copurification and tripartite GFP techniques. Finally, to address the critical need for rapid nanobody design, highlighted by the recent pandemic, we applied our hybrid-AI approach to novel scaffolds generated by RFDiffusion to engineer a nanobody targeting the receptor-binding domain (RBD) of the SARS-CoV-2 XBB1.16 variant. Its high specific binding affinity was experimentally validated, demonstrating its therapeutic potential.

*Speaker

Leveraging computational methods for protein engineering

Jelena Vucinic* [1]

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The landscape of protein engineering is evolving rapidly, driven by cutting-edge computational techniques that are transforming biopharmaceutical discovery and optimization. Engineering biologic drug candidates to optimize desirable properties or reduce unwanted characteristics often requires extensive experimentation. In this talk, we will explore groundbreaking methods that enable accurate modeling of critical physical endpoints, including thermal stability, protein-protein binding affinity, pH sensing profiles and developability risks. These innovations promise to accelerate early-stage discovery while enhancing the precision of biotherapeutic design. We will highlight recent advances in computational structure-based methods and their role in expediting candidate optimization.

*Speaker

11th June 2025

Session 2: Structural Bioinformatics and AI

8:30-10:00

Invited Speaker: Vaitea Opuu

Bridging machine learning and biophysics to expand RNA functional diversity

Vaitea Opuu * [1]

[1] Laboratory of Biophysics and Evolution, ESPCI, CNRS, Paris

The RNA world hypothesis suggests that RNA once catalyzed reactions now performed by proteins. Rediscovering these functions requires exploring sequence spaces beyond natural RNAs. While machine learning (ML)-based RNA design shows promise, it struggles to extrapolate beyond the input training data. In contrast, biophysics-based approaches leveraging RNA structure operate independently of training data but are not tailored for functional discovery. I present a hybrid generative model that combines a Potts model with the thermodynamic folding model of RNA secondary structure. This approach disentangles folding contributions from functional signals, such as binding, enabling the data-driven component to focus on tertiary interactions and improving contact predictions. This disentanglement introduces structural imprinting—a novel strategy that uses structural variability to guide mutations, which showed great promise in uncovering hidden natural diversity. By bridging ML and biophysics, this model tackles the longstanding challenge of expanding diversity beyond the mere reproduction of the training data.

*Speaker

Advanced molecular dynamics simulations and AI for investigating and modulating ABC transporters

Ahmad Elbahnsi * [1] Balint Dudas[2] Salvatore Cisternino[3] Xavier Decleves[3] Maria Miteva[1]

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ATP Binding Cassette (ABC) transporters are crucial for cellular detoxification and the transport of a diverse range of substrates, including drugs. Their roles in multidrug resistance (MDR), drug-drug interactions (DDIs), and severe genetic diseases make them key targets for therapeutic intervention. Structurally, they are organized into two halves, each consisting of a transmembrane domain (TMD) responsible for substrate transport and a nucleotide-binding domain (NBD) that binds and hydrolyzes ATP controlling the transport cycle. To ensure their function, these transporters switch between inward-facing- (IF, with separated NBDs) and outward-facing- (OF, with paired NBDs), open and occluded states.

We developed enhanced sampling methods to investigate these conformational transitions at molecular level. For ABCG2/BCRP (Breast Cancer Resistance Protein), involved in MDR and DDIs, our kinetically excited targeted MD (ketMD) simulations revealed key intermediates in the transport cycle, including a novel substrate-binding pocket between the two established cavities that regulates substrate progression. Furthermore, we demonstrated that substrate presence in the first cavity is essential for synchronizing the NDB-TMD movements, facilitating efficient substrate transport (1). For ABCB1/P-gp (P-glycoprotein), another MDR- and DDI-associated transporter, we implemented an adiabatic biased MD (ABMD) protocol to elucidate the ligand entry, translocation, and inhibition mechanisms. Our results demonstrated that the conformational transitions between IF-open, IF-occluded, and OF states are controlled by specific structural events, notably the kinking and unkinking of particular TM helices. Inhibition of P-glycoprotein was suggested to occur by disrupting the communication between the TMDs and NBD2, preventing the conformational transitions necessary for substrate efflux (2).

Building on these MD simulations, we are integrating the enhanced sampling data into machine learning and deep learning frameworks to develop predictive models for identifying potent inhibitors of BCRP and P-gp, aiming to address therapeutic challenges associated with MDR and transporter-related diseases.

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*Speaker

A Single Framework to Accurately Predict Multiple Impact of Genetic Variants

Ragousandirane Radjasandiran * [1] Julien Diharce [1] Jean-Christophe Gelly [1] Alexandre G. De Brevern [1]

[1] Université Paris Cité, BIGR, DSIMB Bioinformatics team

Amino acid substitutions in protein sequences are generally without consequences, but some of these can trigger diseases. Accurately predicting the impact of such genetic variants can be essential for clinicians and should speed up the diagnosis of new missense variants that may lead to disease. These mutations can have a large panel of effect in several biological processes such as perturbing protein thermal stability or modulate protein-protein interaction, which can ultimately contribute to the pathogenicity of the variant. All information that can arise from a new characterized variant is therefore of importance to help the diagnosis. Nowadays, a multitude of computational tools have been developed with the aim of predicting the pathogenicity of genetic variants using several strategies. There are also methods to predict the impact of variants on protein thermal stability and on protein-protein interaction. However, there are no methods that predict these three features at once, while an unified approach that can be used by clinicians and non-experts would be really useful. Actually, three different and separate tools must be used to get the prediction on pathogenicity, thermal stability and protein-protein interaction, which can be an issue for the non-specialist who are not familiar with bioinformatics techniques.

From this perspective, we wanted to explore the potential of Protein Language Models (PLMs) to predict the pathogenicity of genetic variants and also their impact on protein thermal stability and on protein-protein interaction in one single approach. PLMs have recently shown great promise in the field of protein related tasks, such as accurately predicting amino acids properties, protein function and protein structure from a sequence context. Here, we have first combined several state-of-the-art PLMs, including ProtT5, ESM2, ESMC, and Ankh, to predict the impact of variants on pathogenicity using two high quality datasets, including ClinVar. Our approach reached state-of-the-art performance with MCC values of 0.81 and 0.585 on both datasets, beating several popular tools such as AlphaMissense or EVE. We then attempt to build a unique framework to assess not only the impact of variant on pathogenicity but also on thermal stability and protein-protein interaction affinity. We will present our preliminary results on this combined innovative model.

To the best of our knowledge, this is the first method that achieves competitive performance across all three impacts considered using one unique framework.

*Speaker

Molecular modelling of an intrinsically disordered protein (IDP), human endosulfatase 2 (HSULF2)

Jianjun Tao * [1] Nathalie Basdevant [1]

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In 2002, a new category of two human sulfatases (HSULF1 and HSULF2) was discovered. These enzymes, known as endosulfatases, carry out their enzymatic activity within the heparan sulfate substrate, unlike previously known sulfatases hydrolyzing sulfate groups at the substrate's extremities [1]. Human endosulfatase 2 (HSULF2) consists of three domains: the catalytic domain (CAT), the hydrophilic domain (HD), and the C-terminal domain (C-ter). The pro-enzyme is cleaved in HD by furin protease to be converted into its mature form. Two HSULFs proteins tend to form a dimer. HSULF2 is found to be overexpressed in numerous diseases, particularly breast cancer and inflammation, making it a promising therapeutic target. Structural exploration of HSULF2 is essential to design inhibitors as potential anticancer drug candidates.

However, little is known about the 3D structure of HSULF2: on one hand, no experimentally resolved structure of HSULF2 has been yet uploaded in the Protein Data Bank (PDB); on the other hand, the predicted structure of HSULF2 by AlphaFold2 (AF2) shows a low confidence score, essentially in the hydrophilic domain. The difficulty in obtaining a reliable structure arises from HD, as it is (1) considered an intrinsically disordered region (IDR) and (2) has low homology to all known proteins. Therefore, structural investigation of HSULF2 remains challenging both experimentally and computationally.

In this context, we aimed to predict the 3D structures of different forms of HSULF2 (pro-enzyme, monomer, and dimer) as well as with other post-translational modifications (PTMs), such as modification of cysteine, using state-of-the-art deep-learning based structure prediction algorithms, for example, AlphaFold3 [2], Chai-1 [3] and Protenix [4]. Furthermore, this modeling research is closely integrated with and fed by experimental data obtained from structural and functional characterization carried out in our laboratory using biochemical and analytical chemistry tools, particularly mass spectrometry [5-6], and biophysical tools.

Thus, we benchmarked these structure prediction methods on their capacity to predict low homology and highly disordered regions. We also analyzed the effects of diverse post-translational modifications (PTMs) on the structural organization.

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*Speaker

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Study of the Interaction Between MSMP and CCR2 Proteins using molecular dynamic simulations and machine learning

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[2] Centre Hospitalier Université Laval, Canada
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The MicroSeMinoprotein (MSMP), also known as Prostate Associated Protein, is overexpressed in various cancers, including prostate, ovarian, and breast cancers. Its overexpression has also been observed in cases of resistance to hormone-based chemotherapies, particularly anti-VEGF (Vascular Endothelial Growth Factor) therapies. In VEGF therapy-resistant tumors, MSMP overexpression is thought to be triggered by the hypoxic microenvironment characteristic of certain solid tumors.

MSMP has been shown to bind to the transmembrane receptor C-C chemokine receptor type 2 (CCR2), a G protein-coupled receptor (GPCR) present on the surface of monocytes and lymphocytes. This binding activates the MAP kinase signaling pathway, which in turn reinitiates hormone synthesis, enabling tumor growth (Mitamura et al., 2017).

This study aims to characterize the interaction between MSMP, CCR2, and its associated G protein. The MSMP-CCR2-G protein complex was predicted using AlphaFold-Multimer (Evans, R. et al., 2021), embedded into a plasma membrane, and its stability analyzed through molecular dynamics simulations using the Amber software suite (D.A. Case et al.,2023). In parallel, we investigated another known CCR2 ligand, C-C motif chemokine 2 (CCL2), using the same protocol to assess whether MSMP and CCL2 activate CCR2 through similar mechanisms. Residues involved in the interaction between MSMP or CCL2 with CCR2, as well as the activation mechanism of CCR2, were identified using an AI-based analysis program developed in our laboratory, named BioDiscML.

*Speaker

11th June 2025

Session 3: Visualization, Graphism and Drug Design

10:30-15:00

Keynote Speaker: Barbora Kozlikova

Invited Speaker: Nathalie Lagarde

Keynote 3: Design of Visualization Support for Molecular Visualization

Barbora Kozlikova * [1]

[1] Faculty of Informatics, Masaryk University, Brno, Czech Republic

In my talk, I will present the basic visualization principles typically used in molecular visualizations. Then, I will present examples of designing visual representations for complex molecular data, where the complexity spans from the extensive amount of parameters that should be visually communicated and understood [1], to techniques to handle long molecular dynamics simulations [2,3]. The goal of this talk is to present the basics of a typical workflow of a visualization researcher working in the molecular visualization domain and how this is applied to specific use cases.

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*Speaker

In sillico studies of a membrane transporter involved in antibiotic resensitization

Côme Ghadi * [1] Charline Kieffer [1] Johanna Giovannini [1] Peggy Suzanne [1] Aurélie Verneuil [2] Nicolas Verneuil [2] Axel Hartke [2] Alexandre Mahe [2] Jana Sopkova-De Oliveira Santos [1]

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Antibiotic resistance represents a major public health challenge globally, resulting in a significant increase in the number of deaths and socioeconomic costs associated with infections. In response to this threat, the WHO published a list of twelve priority families of multidrug-resistant microorganisms in 2017 (1). Among these, Gram-positive cocci bacteria, such as Staphylococcus aureus and Enterococcus faecium, were highlighted. While some antibiotics remain effective against these pathogens, therapeutic options are limited. Recent studies suggest that targeting the D-alanylation of TAs could help restore antibiotic sensitivity (2). TAs are essential components of Gram-positive bacterial cell walls, playing a key role in cellular stability by anchoring peptidoglycans to the plasma membrane. The phosphate groups in TAs carry a negative charge, which is partially neutralized by the addition of D-alanine. This modification creates an electrochemical barrier that helps bacteria resist positively charged antibiotics (3). The D-alanylation of teichoic acids (TAs) is mediated by proteins encoded by the dlt operon (d-alanyl-lipoteichoic acid operon), including DltA, DltB, DltC, DltD, and DltX (4). Our study focuses on DltB, a transmembrane transporter with a catalytic histidine that plays a crucial role in this process. In addition to directly contributing to TA D-alanylation, DltB also facilitates the transport of D-alanine from the intracellular environment to the extracellular space in coordination with other dlt operon proteins. Currently, only two DltB inhibitors have been documented in the literature (5,6). The only in vivo inhibitor, Amsacrine, is highly toxic to humans, making it unsuitable as a therapeutic agent. Given the urgent need for novel antimicrobial strategies, our study focuses on the structural and functional characterization of DltB, particularly its binding pockets, with the goal of designing new, effective inhibitors against DltB in Gram-positive cocci.

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*Speaker

UnityMol-Lite: Cross-platform Collaboration and Interactive Methods for Molecular Modeling in Extended Reality

Mariano Spivak * [1] [2] Bastien Vincke [3] [4] Hubert Santuz [2] Jérôme Hénin [2] Antoine Taly [2] Marc Baaden [2] Nicolas Férey [1]

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Molecular modeling plays a crucial role in material science, pharmaceutical research, and biomedical applications, with interactive molecular dynamics (IMD) providing real-time interaction with molecular systems. However, conventional IMD techniques are often limited by their precision and usability in advanced research. Extended reality (XR) technologies offer new opportunities for molecular modeling by enabling natural 3D visualization, intuitive interaction, and real-time collaboration. In this work, we present **UnityMol-Lite**, an optimized, cross-platform version of UnityMol designed for standalone head-mounted displays (HMDs) and collaborative XR experiences. The application integrates a novel interaction technique inspired by tangible interfaces, allowing users to manipulate molecular structures more effectively. This approach leverages **MDDriver** and **COLVARS** to compute forces dynamically, providing a seamless and immersive IMD experience. Additionally, UnityMol-Lite supports **a physical molecular interface**, expanding its applicability for molecular modeling and education. The platform also features an **XR-native user interface** designed for accessibility, ensuring an intuitive experience across expertise levels. With cross-platform compatibility and Photon Unity Networking for real-time collaboration, UnityMol-Lite represents a significant advancement in interactive molecular modeling in XR.

*Speaker

Unveiling G-Protein-Coupled Receptor Conformational Dynamics via Metadynamics Simulations and Markov State Models

Rita Ann Roessner * [1] Nicolas Floquet [1] Maxime Louet [1]

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G protein-coupled receptors (GPCRs) are key players in signal transduction and as such are involved in most physiological and pathological processes. As GPCRs are the most represented protein family among membrane receptors, they are responsible for cellular responses to a variety of different stimuli, including hormones, neurotransmitters, and exogenous substances. It is estimated that one-third of approved pharmaceutical drugs target GPCRs [1]. Since the dynamic character of GPCRs is essential to their functionality, knowledge about their conformational ensembles may improve computer-aided drug design and discovery [2], [3]. To address this question, we developed a generally applicable protocol that combines bias-exchange metadynamics simulations and Markov state modeling to efficiently explore the conformational landscape of the ghrelin receptor, a prototypical class A GPCR [4]. Applying our method, we computed the free energy landscape of the ghrelin receptor in its apo state and bound to pharmacologically distinct ligands. Consistent with the current multi-state model of GPCR activity [5], we show that the ghrelin receptor populates multiple metastable states whose energies and transition probabilities change depending on the bound ligand. Furthermore, our results reveal intermediate states that were not previously described by experimental structures and that we can link to different functions during signal transduction. Due to its applicability to all class A GPCRs our protocol may be a valuable tool for the development of pharmaceuticals targeting this protein family.

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*Speaker

Invited 3: Targeting IL-4/IL-13 Protein-Protein Interactions to Develop Small-Molecule Therapies for Asthma

Nathalie Lagarde * [1]

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Asthma is a complex and heterogeneous disease that can be subdivided into multiple phenotypes based on clinical, physiological, and inflammatory markers. This heterogeneity leads to variable treatment responses, with some patients experiencing severe asthma that is refractory to standard therapy. Novel therapeutic approaches for these patients include dupilumab (1), a human monoclonal antibody targeting IL-4Rα (interleukin-4 receptor α), allowing the simultaneous inhibition of IL-4 (interleukin-4) and IL-13 (interleukin-13), two key cytokines in the pathophysiology of asthma. Small-molecule protein-protein interactions inhibitors (SM PPII) are of great interest in comparison with monoclonal antibody and could complement dupilumab in the treatment of asthma. At the end of 2020, the first and, to date, only IL4-IL13 SM PPII, named N52, was reported (2) and characterized through a combination of binding and functional cellular assays. However, its potential binding site on the IL-4/IL-13 complexes has not been investigated.

To discover new IL-4/IL-13 SM PPII, we developed a dedicated IL-4/IL-13 in silico screening protocol based on protein-ligand docking (3). First, we identified druggable pockets shared between IL-4 and IL-13 complexes with their co-receptors. A repositioning study was then conducted using over 9000 approved drugs. The top 50 compounds identified through this in silico protocol were selected to be tested in an ELISA-like IL-4 and IL-13 binding inhibition assays alongside the reference compound, N52.

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*Speaker

ComPASS, an efficient method to reveal communication pathways within protein-nucleic acid complexes

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Inter-residue communication forms a vast and intricate network that underpins essential biological processes such as catalysis, gene expression, and cell signaling. Allostery, a crucial phenomenon where distant regions of a macromolecule are energetically coupled to elicit functional responses, operates through these intricate communication networks within macromolecular complexes. Despite the pivotal role of nucleic acids in these networks, their contributions to allostery remain largely overlooked. To address this gap, we developed ComPASS, a large-scale computational method designed to study communication networks in protein-protein and protein-nucleic acid complexes. Recognizing the significance of dynamics in the communication of macromolecules, our approach leverages molecular dynamics (MD) simulation data to extract inter-residue key properties, including dynamical correlations, interactions, and distances. These properties are integrated to construct a weighted communication network that comprehensively represents dependencies among amino acids and nucleotides. Using ComPASS, we uncovered distinct mechanisms of signal transmission in diverse macromolecular systems. In Cysteinyl-tRNA synthetase, the central domain was found to mediate the coordination between substrate recognition and enzymatic activity, ensuring functional precision. In the LacI repressor, allosteric communication occurs through interface pathways within the dimer, effectively linking ligand sensing to DNA binding. For the Type IIF restriction endonuclease Bse634I, structural communication across dimer and tetramer interfaces was crucial for specific DNA recognition. In the liver X receptor, a key helical region was identified as a bridge connecting ligand-binding events to DNA interactions. Finally, our analysis with ComPASS aligned with previous literature, confirmed the role of H2A L1 loops in mediating communication across histone interfaces and coordinating interactions between structural domains in nucleosome complexes. ComPASS is available as an open-source tool, maintained at https://github.com/yasamankarami/compass. By offering an integrated framework for studying communication networks, ComPASS advances our understanding of conformational dynamics, particularly within protein-nucleic acid complexes.

*Speaker

Designing of novel broad spectrum antivirals

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Picornaviridae family includes different genus of RNA viruses. One of them, the Enterovirus genus, comprises four enterovirus (EV) species (A, B, C and D), three rhinovirus (RV) species (A, B and C) as well as non-human enteroviruses.(1) Human EV species such as coxsackieviruses (EV-A to EV-C) and echoviruses (EV-B) are highly related to hand, foot and mouth disease (HFMD), and also involved in conjunctivitis and viral myocarditis. HFMD affects mainly children under 5 years old and can lead to serious complications like aseptic meningitis, acute flaccid paralysis or fatal respiratory disease. In the market, one effective vaccine is available against poliovirus. Another vaccine for enterovirus A 71 (EV-A 71) serotype was developed, but only approved in China.(2) So, developing broad spectrum antivirals will be of high interest to target the different species of the genus and also to overcome the diversity of serotypes within each one.

Structurally, the EV genus is constituted of seven non-structural proteins and four structural proteins where the 2C protein one is the most conserved among them. This latter, formed of a N-terminal membrane-binding domain, a central ATPase domain, a cysteine-rich domain and a C-terminal helical domain, is currently considered as a promising therapeutic target due to its ATPase function implicated in viral replication.(3) First screening series have shown an ex-vivo anti-enterovirus activity of about twenty molecules, but the relevant toxicity reported for some of them like Guanidine HCl, have restrained their development.(4) More recently, a repurposing strategy has been adopted and Fluoxetine (Prozac®) was identified as a replication inhibitor of human enterovirus A, B and D species with no toxicity issues. Used for depression and acting as selective serotonin reuptake inhibitor, Fluoxetine contains a chiral quaternary carbon centre and only the S-enantiomer seems to show a biological activity against 2C protein.(5) Other published Fluoxetine analogs have also confirmed in-vitro biological activities on 2C protein, but their antiviral activity was still limited.(6) Structurally, recent study has solely co-crystallized (S)-Fluoxetine with 2C protein, revealing a new allosteric binding site.(3)

Hence, in order to enhance the potency of Fluoxetine analogs towards 2C protein and enlarge the targeting spectrum of designed molecules, we relied on a diverse panel of structure-based drug design and chemoinformatics tools to design novel non-covalent inhibitors, by substituting the different motifs of Fluoxetine as well as its central core encompassing the chiral carbon atom. The synthesis of the best non-covalent molecules showed a promising broad anti-enteroviral activity. However, the exact mode of action relevant to both enantiomeric isomers of Fluoxetine is still ambiguous.

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TNFα:TNFR1 complex in a membrane context: structural and functional insights

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Tumor Necrosis Factor alpha is a pro-inflammatory cytokine essential to balance life and death of cells. In some circumstances, TNF-alpha can trigger too important inflammation leading to inflammatory diseases such as Inflammatory Bowel Desease (IBD). By experimental means, many studies have deciphered at the atomistic level how TNF-alpha binds to its receptor TNF receptor 1. The influence of the membrane context for the cytokine-receptor complex is lacking experimentally. In our study, we used advanced molecular dynamics simulations to understand how lipid-mediated interactions can influence the binding partners. We identified numerous residues present on the cytokine and the receptors, highlighting key residues important for the cytokine activity. Our study could recover and explain the role of many residues, and provides a new insight into the importance of new amino acids on the structure and function of the complex. These findins shall allow further experimental exploration of the binding interface.

*Speaker

Efficient compound selection strategies in lead optimization: insights from retrospective analysis

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In the Drug Discovery pipeline, the lead optimization stage is devoted to the multi-parametric optimization of a small set of lead compounds identified at the previous stage of the process. Within the Design-Make-Test-Analyze (DMTA) paradigm, the lead optimization takes place through an iterative process where new molecules are proposed and selected for synthesis at the "Design" stage of each DMTA round. This iterative selection process is akin to Active Learning (AL), a subfield of Machine Learning (ML) in which an algorithm selectively queries unlabeled samples to optimize model training.

AL algorithms have been applied to the iterative selection of molecules during virtual screening for hit identification (1,2), but their application at the lead optimization stage present significant challenges. One of them is that the pool of molecular hypotheses to choose from at each round of selection is dynamic, contrary to the lead finding stage where the chemical space of hypotheses to be selected is static. Additionally, lead optimization entails a multi-objective optimization, where potency must be balanced with selectivity and ADMET properties, further complicating the application of AL in this context.

We developed a multi-objective compound prioritization toolkit that integrates a set of selection strategies inspired by AL algorithms, multicriteria decision methods, and classical medicinal chemistry strategies. On top of this toolkit, we developed an analytical framework that quantitatively and qualitatively characterizes the exploitation and exploration capabilities of these strategies. We used this toolkit on a dozen of legacy industrial lead optimization projects to evaluate retrospectively the performance of these selection algorithms.

In this contribution, we present our analysis of these retrospective simulations to uncover the distinct behaviors of different selection strategies. Our findings highlight that while some strategies excel at rapidly identifying the best compounds, they do so at the expense of a less thorough exploration of the chemical space. Furthermore, we demonstrate that commonly used evaluation criteria for selection strategies can be misleading.

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*Speaker

11th June 2025

Session 4: Integrative modeling

15:00-18:30

Keynote Speaker: Massimiliano Bonomi

Invited Speaker: Claire de March

Keynote 4: Structural and dynamic biology with integrative approaches

Massimiliano Bonomi* [1]

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Understanding the molecular mechanisms by which biological systems carry out their functions is often essential for the rational targeting of associated diseases. In many cases, determining the three-dimensional (3D) structure of these systems provides valuable insights. However, it is often the interplay between structural and dynamical properties that determines the behavior of complex systems. While both experimental and computational methods are invaluable for studying protein structure and dynamics, the limitations of each individual technique can hinder their capabilities [1].

Here, I present our lab's work on developing integrative computational-experimental approaches that combine experimental data with molecular dynamics (MD) simulations to determine accurate protein structural ensembles of biological systems [2,3]. I will showcase the capabilities of these methods through various applications to systems of significant interest. First, I will demonstrate how accurate protein structural ensembles can be obtained from 3D cryo-electron microscopy maps using our recently developed EMMIVox approach [4]. Then, I will highlight how we characterize the structural and dynamic properties of the CyaA toxin by integrating coarse-grained MD simulations with Hydrogen/Deuterium eXchange Mass Spectrometry (HDX-MS), Small-Angle X-ray Scattering (SAXS), and 2D single-particle cryo-EM data. Finally, I will show how structural information provided by Artificial Intelligence approaches, such as AlphaFold, can be synergistically combined with low-resolution experimental data to generate accurate models of protein complexes.

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*Speaker

Auto-Martini Update for Martini 3: Still Fast and Furious, Now More Accurate and Versatile

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The release of the Martini 3 Force Field enables precise coarse-grained parametrization, capturing fine-scale features essential to model small molecules. However, advancements in Martini 3 methodology also increase the difficulty of manually implementing these new rules to coarse-grained modeling.

Here, we present Auto-MartiniM3, an updated version of Auto-Martini, designed for the automatic coarse-graining parametrization of small molecules with up to 20 heavy atoms within the Martini 3 Force Field.

To validate Auto-MartiniM3, we have tested it on 85 small molecules from the Martini Database, parametrising them and simulating in various solvents and assessing their physicochemical properties against experimental data.

We used the Adenosine A2A receptor, a GPCR, and its antagonist, caffeine, to demonstrate the tool's practical application in biomolecular simulations. We successfully simulated the coarse-grained protein-membrane-ligand system and observed the expected binding behavior. Our results confirm that Auto-MartiniM3 performs reliably across diverse molecular systems, providing an efficient and accurate solution for high-throughput coarse-graining of small molecules.

*Speaker

Bayesian Analysis of Constant pH MD and Protonation Couplings

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The protonation states of titratable groups, through their effects on electrostatics and hydrogen bonding networks, are highly relevant for the structure and function of biomolecular systems, from enzyme catalysis to tertiary structures. Far from being a static property, protonation is dynamic and depends on conformation and protonation states of other residues; vice versa, it drives structural rearrangements and protonation change. Molecular dynamics (MD) simulations typically employ fixed protonation states, an approximation that fails to capture this interplay. We overcome this limitation using a Fast Multipole Method-based[1] lambda dynamics[2] approach implemented in GROMACS,[3,4] developed within our research group. This constant pH MD (CPH-MD) method dynamically changes residue protonation during simulations, generating conformational trajectories, time-dependent protonation states, and enabling computational titration, i.e. simulation at different pH values, for pKa determination. Traditional analyses of CPH-MD data typically rely on Least Squares fitting to extract apparent pKa values from such titration curves, sometimes combined with techniques like Functional Mode Analysis.[2] These approaches provide valuable insights into individual residue titration but struggle to account for protonation-conformation coupling or cooperative effects, particularly when both occur simultaneously. We propose a Bayesian framework as a robust and rigorous alternative for analyzing constant pH MD data. This approach provides several key advantages: it quantifies uncertainty through posterior distributions; its forward model readily incorporates protonation-conformation coupling, residue-residue cooperativity, and non-Henderson-Hasselbalch behaviors; it allows integrative modeling, for instance combining NMR titration data that provide reliable ensemble average pKa with the microscopically detailed but sampling-limited picture of CPH-MD protonation. We demonstrate this novel approach on three benchmark proteins with measured pKa values and extensive CPH-MD simulations, modeling conformation-protonation coupling in those proteins through a hidden process (e.g., random walk, Gaussian process, or Brownian dynamics), quantitatively characterizing the influence of the residue environment.

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*Speaker

HADDOCK3, a modular platform for biomolecular integrative modelling

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Predicting biomolecular interactions remains a significant challenge in structural biology due to macromolecule's inherent complexity and flexibility and the need to integrate diverse experimental and computational data. While AI-driven methods like AlphaFold have revolutionized structure prediction, physics-based approaches offer unique advantages, particularly in capturing molecular dynamics and integrating experimental restraints. Integrating experimental data into the modeling process is a fundamental principle of the HADDOCK software, which employs ambiguous interaction restraints (AIRs) to guide physics-based docking towards models that best align with the provided data. HADDOCK3 rises to these challenges with a modular, Python-based framework that supports highly customizable docking and multicomponent assembly workflows. Building on the robust foundation of its predecessor, this new version enhances parallelization, optimizes performance, and incorporates experimental data from techniques such as NMR and SAXS. With the ability to customize every step of the pipeline—from topology generation to scoring and refinement—HADDOCK3 ensures flexibility to meet diverse research demands. It is a transformative tool for both focused and large-scale docking studies, advancing our understanding of the molecular basis of biomolecular interactions. This presentation will delve into its innovations, features, and contributions to structural biology.

*Speaker

Structural elucidation and molecular mechanisms of mammalian odorant receptors

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Odor perception is based on odorant receptors (ORs), which belong to the large family of G protein-coupled receptors and more particularly to the rhodopsin-like family, also called class A. The vast majority of odorant receptors show poor cell surface expression in non-olfactory cells due to retention of the endoplasmic reticulum (ER), hindering their structural elucidation and functional study. Here, we study at the molecular level the expression mechanisms of this sub-family of G protein-coupled receptors. In this project, we use the diversity of the odorant receptor repertoire to create new optimized synthetic receptors based on their consensus sequences. Using these consensus ORs, we study the role of amino acids in their expression through molecular modeling, site-directed mutagenesis, and flow cytometry. Their functionality is also assessed by *in vitro* assays. We recently obtained the first structural elucidations of mammalian ORs in cryo-EM, allowing us to explore the structural diversity of ORs in molecular dynamics simulations. This research is crucial, not only to understand the strategy of our brain to perceive its olfactory environment but also to identify general mechanisms governing the function of ORs.

*Speaker

Water Molecules as Molecular Probes: Understanding and Reshaping Enzyme Interiors

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Water molecules maintain enzymes' structures, functions, stability and dynamics. Therefore, they are ideal probes for investigation of enzymes' properties which allows us to understand the mechanisms responsible for macromolecules interactions, signal transduction and catalysis. The analysis of water molecules' distribution and trajectories allows to study proteins' interactions with small molecules, dynamic shape of the tunnels and cavities network, its functionality, and location of key residues controlling transportation through such a network. Studies of the dynamics of tunnels, cavities and other types of intramolecular voids buried inside macromolecule's core remain a challenging task due to the ephemeral character of these elements. Moreover, the experimental methods hardly provide insight into accessibility of such structures, transport of small ligand(s) or solvent exchange between protein interior and the environment. AQUA-DUCT, an open-source Python software, permits to track small molecules and analyse their transports, and access information about residues controlling access to the active site and regions in which small molecules are stuck or trapped during MD simulation.(1-2)

A comprehensive overview of several studies performed by our group in the last years using AQUA-DUCT which provides insight tunnel network and evaluation of enzyme engineering will be presented.(1-3) By combining MD simulations with our software, we got access to information about flow direction, and regions in enzymes in which small molecules are stuck or trapped. By analysing the local distribution analysis, we were able to determine the approximate energy profile of a particular passage and finally understand changes in enzyme performance due to particular mutations. The extensive comparison of interior dynamics within the enzyme family helps us to understand tunnels network evolution. The analysis of the protein interior from the perspective of water molecules can be used as a versatile and exhaustive approach that enables enzymes understanding and re-engineering.

Acknowledgements

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Unraveling the Impact of Cofactors on the Dynamics of BVMO enzymes.

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Baeyer-Villiger Monooxygenases (BVMOs) are flavoprotein enzymes that play a critical role in the selective oxidation of ketones to esters, with applications spanning biocatalysis and pharmaceutical manufacturing. Their enzymatic activity relies on two essential cofactors: flavin adenine dinucleotide (FAD) and nicotinamide adenine dinucleotide phosphate (NADPH). While previous studies have provided insights into the static structure of BVMOs, the dynamic contributions of FAD and NADPH to enzyme conformational flexibility and catalytic efficiency remain poorly understood.

In this study, we used molecular dynamics (MD) simulations to investigate the structural and dynamic impact of these cofactors on the cyclohexanone monooxygenase (CHMO) from *Rhodococcus sp.HI-31*. We analyzed four distinct systems: the enzyme alone, the enzyme with FAD, the enzyme with NADPH, and the enzyme with both cofactors. Comparative analyses of MD trajectories, using both classical and innovative approaches such as the Protein Block's structural alphabet, revealed distinct conformational changes influenced by cofactor binding, including variations in active site geometry, domain movements, and overall protein flexibility. When bound individually, FAD and NADPH produced unique dynamic behaviors, while their combined presence highlighted cooperative effects on enzyme stability and flexibility.

This work provides a deeper understanding of the structural dynamics underlying cofactor-enzyme interactions. These insights, combined with our previous evolutionary study of amino acid conservation within the BVMO family and enzyme design efforts on BVMO4 from *Dietzia*, could help guide future protein engineering efforts aimed at enhancing BVMO efficiency for industrial and pharmaceutical applications.

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*Speaker

Kinetics rates calculations of β2-adrenergic receptor-ligand assemblies

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The association/dissociation of ligands to/from proteins are key biophysical events in cells. Beyond thermodynamic characterization, understanding kinetics helps to improve the knowledge of these key interactions and is crucial for drug development (1). A longer residence time (τ_{res}) of a drug correlates with a prolonged effect. The dissociation rate constant (k_{off}) is the inverse of τ_{res}, and the association rate constant kon is related to the inverse of the association time τ_{on}. These parameters can be obtained through simulations (2), though long timescales often require biased MD methods.

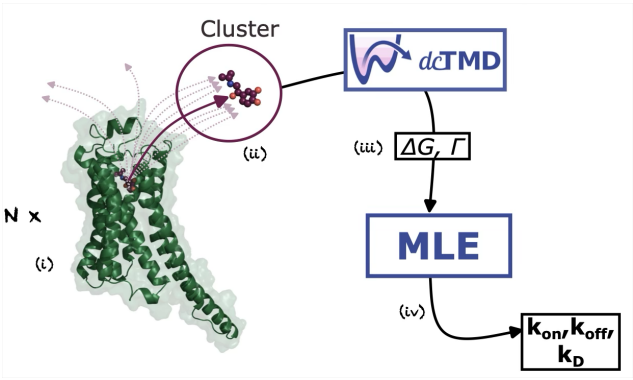

Figure - dcTMD strategy, (i) Hundreds all-atoms MD simulations are performed, (ii) Clustering to determine release pathways,(iii) Clusters are input in dcTMD, to compute the energy and friction, (iv) k_{on} and k_{off} are compute using Markovian Langevin Equation.

This work computes kinetic rate constants for four catecholamine ligands (three agonists and one antagonist) of the β2-adrenergic receptor, a GPCR. Ligand binding/unbinding occurs via metastable states (3), essential for accurate kinetic estimation. We applied dcTMD (4), a method using pulling MD simulations to determine unbinding pathways, friction factors, free energy, and kinetic constants (*Figure 1*). Hundreds of pulling simulations (of about hundreds nanoseconds each) were performed for each ligand, followed by trajectory clustering to define the unbinding pathway. Kinetic and thermodynamic quantities were computed using a Markovian Langevin equation (4). The clustering step is crucial and represents the most challenging part of the project. Several approaches have been proposed to find the most accurate way to cluster the trajectories using

*Speaker

data science tools. Our results align with experimental evidence (5,6), confirming that dcTMD is effective and computationally affordable for computing GPCR-ligand unbinding kinetics. The fact that enhanced MD simulations are able to compute kinetic rates could open new opportunities in drug development, especially considering that this approach works with GPCRs, a key protein family.

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Structure resolution of glucose units in a heparan sulfate mimetic (RGTA®).

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ReGeneraTing Agents (RGTA®) are synthetic polysaccharides designed to mimic the structural and functional properties of heparan sulfates (HS), essential components of the extracellular matrix that are degraded during tissue injuries. Among them, OTR4120, marketed as the medical device CACIPLIQ20®, is synthesized from a dextran backbone (α(1–6) linked glucose units) and modified through carboxymethylation and sulfation. Due to the statistical nature of these chemical modifications under Good Manufacturing Practices (GMP), slight variations in glucose unit composition between production batches are expected, leading to a heterogeneous distribution of chain lengths and positions of substituents.

To characterize the glucose unit composition and confirm its structural features, the heterogeneity of 10 batches of OTR4120 was analyzed using 1H NMR at 600 MHz by optimizing pressure and temperature conditions to enhance signal resolution. Higher-field NMR experiments (1H-950 MHz, 13C-237 MHz) were combined with Lorentzian deconvolution to quantify the different glucose units, while 13C-HSQC and HMBC at 950 MHz enabled the assignment of signals corresponding to carboxymethyl and sulfate substitutions. In parallel, a molecular dynamics approach was used to study the interaction of OTR4120 representative fragments with FGF-2. Finally, a quantum simulation study was conducted to understand the differences in reactivity of the various hydroxyl positions of glucose.

OTR4120 exhibits molecular weight polydispersity, originating from a 40 kDa dextran precursor corresponding to an average of 247 glucose units. Post-substitution, the polymer presents 27 statistically possible glucose units based on their substituent combinations, rendering full-length molecular dynamics simulations impractical. NMR analyses revealed minimal differences across the 10 GMP batches, confirming molecular homogeneity. Among the 27 statistically glucose unit combinations, only 13 glucose units with various substituent combinations have been observed by NMR. Additionally, no glucose units remained unsubstituted at the C2 position. This quantification enabled the selection of representative tetra-saccharides for molecular dynamics simulations. The dialogue between theory and experiment has provided valuable insights into the structure–property relationships of these sugar assemblies, known for their particularly complex nature.

*Speaker

12th June 2025

Session 5: Multi-scale calculations

8:30-11:35

Keynote Speaker: Aurélien de la Lande

Invited Speaker: Natacha Gillet

Keynote 5: Computer Modelling of Electron Transfers in Complex Biological Structures

Baptiste Etcheverry [1] Xiaojing Wu [1] Raaif Siddeeque [3] Frederic Melin [3] Petra Hellwig [3 4] Marc Baaden [1] Fabien Cailliez [2] Aurélien de la Lande * [2]

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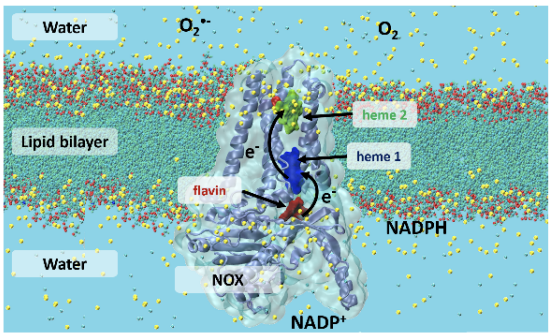
Electron transfer lies at the heart of a multitude of biological processes such as cellular respiration, photosynthesis, immune response and enzyme catalysis. While the physico-chemistry of electron transfer in the biological environment is now well established thanks to the pioneering work of Warshel, Beratan, Gray and many others, much remains to be discovered about how these phenomena interplay within complex biological machineries and couple with the multi-scale processes they are the scene of.

During this conference, I'll be presenting the dedicated developments we've made in the group to model TEs. The quantum nature of electrons means that quantum-mechanical approaches have to be used either to derive theoretical models or to simulate these processes numerically[1]. In particular, we have been working on constrained DFT and hybrid QM/MM schemes[2,3].

I will review several research topics explored by the team using these tools. Firstly, the photoinduced electron transfer cascades in cryptochromes and photolyases, which take place in a few tens of picoseconds[4,5]. These characteristic times are faster than the response times of the protein structure, and push Marcus' theory to the limit. I'll then present more recent results on membrane redox proteins, either transporting electrons across the membrane (NADPH oxidases)[6], or ensuring bacterial respiration by reducing oxygen (cytochromes bd). Our results show how the components of these composite systems work together to control TE thermodynamics and electron tunneling.



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Histidine 73 methylation coordinates β-actin plasticity in response to key environmental factors

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The Actin protein, an important component of the cytoskeleton, is regulated by several environmental factors, such as the ion concentration or the state of the nucleotide in its cavity. The Actin also presents an understudied post-translational modification on its histidine 73, which is methylated (H73C). Using all-atoms (AA) molecular dynamics simulations, adaptive sampling and the AMOEBA polarizable force field, we investigated of this PTM regulates β-actin plasticity in the monomer and filament form. Our results show that H73C changes the dynamics of the protein in presence of ATP and that this effect is reduced in presence of ADP in the monomer form. In addition, the methylation helps stabilizing the barbed end of actin filaments, and slows down the release of the Gamma phosphate of ATP, thus stabilising the filament, as confirmed by microfluidics experiments. Besides the biological effects, the methylation also has to be taken into account when developing Coarse-grained (CG) models of the Actin. By studying the effects on monomers and Actin-profilin complexes, we could show that using the classical workflow to develop CG models, we were not able to reproduce the all-atom fluctuations. By using a structure extracted from AA simulations, we could show that the CG model established would better reproduce the protein fluctuations, as observed at the atomistic level.

*Speaker

Investigating SHAPE chemical reactivity of RNA molecules using a multiscale approach

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RNA molecules play key roles in gene expression, ranging from information preservation to chemical catalysis. Their functions depend on specific conformations and folding patterns, which in turn are governed by the nucleotide sequence and nucleobase interactions. In order to overcome the lack of 3D structures available in databanks, chemical probing emerged, and its data has been integrated into the prediction of 2D and 3D structures. Among these techniques, SHAPE technology has gained widespread use, providing nucleotide-resolution structural information. It employs small electrophilic molecules that acylate the 2'-hydroxyl group, forming a 2'-O-adduct. Although this approach is well established and its dependence on local flexibility is documented, the reasons behind variations in reactivity remain unclear. Several questions about the relationship between structure, conformation, flexibility, and reactivity remain unanswered. To investigate the SHAPE chemical reaction, we focused on a well-known RNA motif, the GAAA tetraloop of the SAM-I riboswitch, and a specific SHAPE probe. First, we characterized favorable and unfavorable binding states using two geometric descriptors in all-atom umbrella sampling (US) simulations . We then employed a semi-empirical quantum mechanical (QM) approach in a multiscale QM/MM description to extend our analysis beyond binding and examine adduct formation. To manage computational complexity, these studies were conducted on the isolated stem loop constituted by 14 nucleotides. The results from classical all-atom biased umbrella sampling simulations served as starting points for QM/MM US simulations. Our findings confirm that SHAPE reactivity is influenced by the local flexibility of different chemical moieties and depends on the relative orientation of the SHAPE probe with respect to the ribose and nucleobases. Finally, we conducted a structural analysis. These results highlight the critical role of the binding process in establishing plausible pre-reactive states that could influence the reaction pathway. They also underscore the need for a more comprehensive understanding of the SHAPE reaction mechanism.

*Speaker

Sampling Effects on Photophysical Properties of Biliverdin in the GAF Domain of Bacterial Phytochrome by Advanced Molecular Dynamics Simulations

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The chromophore-binding domain of phytochromes, GAF domain binds the chromophore biliverdin. Experimental absorption spectra of the chromophore inside the protein are available. Phytochromes, acting as photoreceptors, toggle between states that absorb red and far-red light, with absorption maxima varying by 50 to 70 nm depending on chromophore configuration.

All atoms classical Molecular Dynamics simulations of the chromophore protein complex are carried out first to understand the environment of the chromophore. QM/MM single transitions and QM/MM dynamics are then presented (Amber-Terachem interface). The dynamic effect of protein on the absorption spectra of the chromophore is analyzed. The obtained simulated spectra are compared to the experimental one showing the importance of considering the dynamics of the system.

*Speaker

Invited 5: Multi-scale molecular dynamics simulations for oxidative damages in nucleosomal DNA: from ionization to repair

Natacha Gillet * [1] Maxime Kermarrec [1] Zineb Elftmaoui [1 2] Thomas Boukéké-Lesplulier [1 2] Elise Dumont [3]

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Oxidative stress or ionizing radiation can modify the well-designed structure of DNA by inducing nucleobases lesions. The accumulation of these damages can hinder the DNA transcription or replication and lead to mutations, cell apoptosis or cancers. As a consequence, numerous studies focus on the elucidation of the mechanisms of damages formations or their repair by dedicated proteins. Because of the complexity of the DNA molecule in its biological context, the problem becomes rapidly combinatorial, involving sequence, structural and dynamical effects, for instance to deal with the competition between radical reactivity and charge transfer. Indeed, beyond the double strand structure, the DNA polymer is wrapped around a core of eight proteins call histones to form nucleosomes (1). This specific and dynamical environment mechanically constrains the DNA conformation and creates a heterogeneous electrostatic field, which impacts the redox properties of the nucleobases, their reactivity and their accessibility to protein interacting with DNA. In our group, we mix microsecond timescale classical molecular dynamics and QM/MM calculations to investigate the impact of the nucleosome structure on the formation of oxidative damages on guanines and their repair. We started from the mapping of ionization hotspots in the nucleosome (2), and explored the charge transfer properties of the system. We also explore the dynamics properties before and after the damage formation, focusing on 8-oxoguanine or DNA-protein crosslink (3). Finally, we are performing our first simulations in presence of repair proteins. All along these studies, the role of the nucleosome specific structure has been highlighted with a specific focus on flexible histone tails.

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*Speaker

Multiscale in silico modeling and simulation of an antibody at ultra-low temperatures: impact of cryoprotectants and insights into the dimerization phenomenon.

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Monoclonal antibodies (Mabs) are widely used in biotechnology fields and the pharmaceutical industry. Their ability to bind to specific targets makes them very popular and useful for various purposes. However, even if their production pipeline and design protocols are widely controlled, the aggregation of these molecules is responsible for a loss in production and a risk of loss of function and remains poorly understood. Studies have demonstrated that this phenomenon is prevalent during the conservation steps and freezing/thawing steps of the Mabs when low temperatures conditions are used. The presence of cryoprotectants limits the risks in solution, but are not efficient enough to preserve the function.

In the present work, we used molecular modeling and molecular dynamics simulations to understand the effect of low temperatures and cryoprotectants on the dynamical behaviour of the Pembrolizumab (PMB), a model Mab. PMB is an anti-cancerous IgG4 that targets PD-1 expressed at the surface of tumors, allowing their apoptosis. It was simulated at 253 K in the presence of dimethyl sulfoxide (DMSO) or ethylene glycol (EDO), or water to explore the conformational space within these conditions and the consequences for the aggregation phenomenon. We use a multiscale approach to investigate the putative impact of cryoprotectants on the PMB, combining all-atom simulation to study the monomeric state, and coarse-grained simulation to explore the formation of PMB dimers in these conditions.

Using the all-atom CHARMM36 force field, a total of 3 µs were simulated at 253K for PMB alone and in presence of cryoprotectants. We observe the surprisingly great flexibility of PMB at low temperature in water and the reduction of the fluctuations in the presence of DMSO and EDO. We show how each of these cryoprotectants covered the surfaces of the Mab. During the simulations, new contacts between the different subdomains of the PMB are formed, compared to the X-ray structure. Notably, these interactions involve the Fabs, which contain the CDR regions, and the Fc domain. We hypothesize that these novel contacts within a monomer might be also observed between two monomers. Hence, we examined how two PMB molecules might interact in the same conditions.Thus, we simulated two PMB using coarse-grained MARTINI3 force field, for 20 μs, at 253K with and without the DMSO or EDO. We examined different initial positionings of the two molecules. For each system, two replicates were realized. Independently of the initial conditions, we observed the formation of stable dimers. Interestingly, the sampled dimerization interfaces involved the same regions as identified in the all-atoms simulations.

In summary, we investigated, for the first time, the impact of the presence or absence of different cryoprotectants on the behavior of PMB at the atomic level. We showed that the "Y" conformations observed in the crystallographic model of PMB are not maintained at these temperatures. Interactions between fragments that were initially distant were formed . We were also

*Speaker

able to observe the formation of dimers in these particular environmental conditions that involves interaction between subdomains similar to those formed within the monomer. Most importantly, we demonstrate that these surfaces of interactions do imply CDR and could directly affect the function of the Mab.

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

Abir Kebabsa * [1] François Maurel [1] Éric Brémond [1]

[1] Interfaces, Traitements, Organisation et Dynamique des Systèmes, Université Paris Cité

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 $ADOTA^+$.

*Speaker

Computational prediction of modulatory ligands binding in synaptic receptors

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Nicotinic acetylcholine and Glycine receptors (nAChRs and GlyRs) are pentameric protein assemblies that convert a chemical signal into an ion flux through the postsynaptic membrane. They play a central role in the intercellular communication in the brain and the nervous system and are involved in fundamental processes such as attention, learning, and memory (1). Their pharmacology is currently under development for the treatment of Alzheimer's, Parkinson's, schizophrenia, depression and pain. Recently, an extension of the popular Monod-Wyman-Changeux (MWC) model for the allosteric transitions of synaptic receptors was proposed (2) that expresses important pharmacological attributes such as potency, efficacy and selectivity of the modulatory ligands in terms of the ligand-binding affinity for the active, resting and desensitized states of the receptor. In addition, due to recent improvements in the structural determination of transmembrane proteins, several high-resolution structures of nAChRs and GlyRs in different physiological states and in complex with modulatory ligands have become available (3, 4). The peculiarity of the neurotransmitter-receptor recognition is the presence of essential cation-π interactions in the ligand-binding site. These interactions are difficult to describe with classical force fields, which hinders the possibility of accurate affinity predictions via free-energy simulations. A thorough assessment of the quality of the existing force fields when cation-π interactions are involved is necessary for any rational drug design for brain disorders. The present work took two directions. On the one hand, we found that classical force fields stabilize binding modes for glycine and taurine at GlyR which are different compared to the recently deposited cryo-EM structures. The refinement of their binding pose is essential to reveal the fundamental nature of the neurotransmitter-receptor interaction and assess whether classical force fields are adequate for binding free energy calculations at synaptic receptors. For this purpose, *ab initio* QM/MM molecular dynamics simulations were performed from two cryo-EM structures of GlyR using the MiMiC QM/MM framework (5) and dispersion-corrected DFT functionals, and the QM/MM results were compared with classical MD simulations. On the other hand, the quality of classical force fields could be assessed by comparing calculated ligand-binding affinities at synaptic receptors with experiments. For this purpose, absolute binding free energy (ABFE) calculations were carried out on the acetylcholine binding protein (AChBP), a model system of the extracellular domain of nAChR featuring the same cation-π interactions in the nicotine's binding site. As AChBP is characterized by several X-ray high-resolution structures with ligands as well as high-quality binding affinity data, these calculations allow for a direct comparison with experiments. In this context, the accuracy of different force fields was analyzed. The results of both investigations will be presented at the Conference.

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12th June 2025

GGMM Thesis prize

Exploring the Allosteric Modulation of the Nicotinic Acetylcholine Receptor α7 by Molecular Dynamics Simulations

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The nicotinic acetylcholine receptor α7 (α7 nAChR), a member of the pentameric ligand-gated ion channel superfamily, plays a crucial role in synaptic transmission. This receptor is implicated in a range of diseases, including various neurological disorders and COVID-19, making it an interesting pharmacological target. However, the design of drugs modulating the activity of α7 nAChR is hindered by its exceptionally fast desensitization.

Using all-atom molecular dynamics simulations combined with Markov state modeling, we explored the mechanism of α7 nAChR desensitization and its implication on allosteric modulation. Our initial simulations of cryo-EM structures of the receptor in the desensitized conformation revealed an unexpected plasticity at the level of the ion pore. Further construction of the Markov State Model allowed us to identify two metastable states within the desensitization: open-channel and closed-channel, and to describe the transition mechanism between them. The identification and characterization of the short-lived open-channel intermediate state provided a rationalization of characteristic effects of certain mutations and shed light on the mechanism of action of different positive allosteric modulators of α7 nAChR.

*Speaker

Posters

Poster 01

A MARTINI 3 compatible RNA model to study TDP-43/RNA oligomers

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TAR DNA binding protein (TDP)-43, a nuclear protein involved in RNA metabolism, has been discovered to be the hallmark of numerous neuro-degenerative diseases, including amyotropic lateral sclerosis (ALS), frontotem- poral lobar degeneration (FTLD) and Alzheimer's disease [1]. Despite its pathological significance, key structural properties of TDP-43, such as its folding behavior and oligomerization under disease conditions, remain poorly understood. This challenge mainly stems from its intrinsically disordered C-terminal domain, which represents nearly 30% of the protein and limits structural characterization via traditional techniques like NMR and X-ray crystallography [2].

Experimental studies have demonstrated that the two conserved and ordered RNA recognition motifs (RRM-1 and RRM-2) of TDP-43 bind GU-rich RNA sequences with high affinity [3], preventing its pathological aggregation [4]. However, the molecular details of this RNA-driven antagonistic effect, including the molecular organization between disordered and ordered domains in TDP-43 assemblies, remains elusive. Molecular dynamics (MD) simulations, particularly coarse-grained (CG) approaches, provide a promising avenue to address this gap by enabling long-timescale simulations and capturing multi-protein assemblies, which would be computationally expensive at an all-atom (AA) MD scale [5].

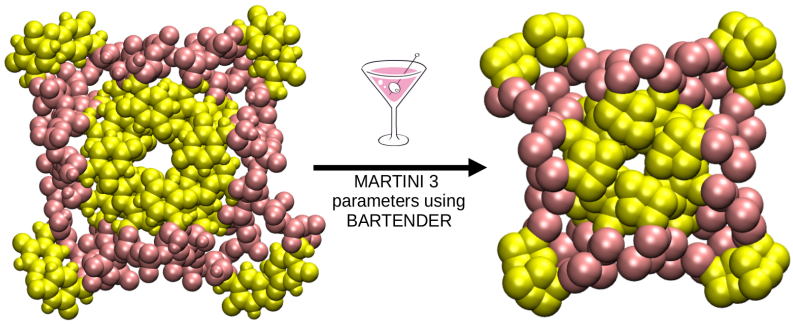

Figure: All-atom and Coarse-grained representations of RNA (GU)12 G-quadruplex, pdb: 8TNS [8]. Phosphate-ribose groups (RNA backbone) and nucleobases are represented in pink and yellow, respectively.

This study therefore aims to investigate TDP-43/RNA and TDP-43/RNA oligomers using MARTINI 3 [6] coarse- grained (CG) force-field, which has been significantly improved for modeling intrinsically disordered proteins and oligomers. Unfortunately, the nucleic acids are not yet available in this new version, requiring the develop- ment of a MARTINI 3-compatible RNA model (See Figure). To achieve this, we are parameterizing GU-rich RNA sequences using BARTENDER [7] and are validating them through comparisons with all-atom simulations performed in our laboratory and experimental data. Once validated, long-timescale CG-MD simulations will be performed to elucidate the structural and mechanistic properties of TDP-43 in complex with RNA.

*Speaker

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Poster 02

AI Diffusion Models for Computational Protein Design

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Protein engineering with tailored properties has significant implications across various fields, including medicine, biotechnology, synthetic biology, and nanotechnology. Structure-based computational protein design (CPD) [1] has become a powerful tool for this purpose. However, CPD presents an inherent computational challenge, classified as NP-hard [2], due to the vast combinatorial space of possible amino acid sequences and their corresponding 3D conformations. In this work, we introduce a novel CPD approach that leverages recent advancements in Artificial Intelligence (AI), specifically neural network-driven combinatorial optimization (CO) techniques. Traditional neural CO solvers fall into three categories: autoregressive constructive solvers, non-autoregressive constructive solvers, and improvement heuristic solvers. Each of these approaches has notable limitations: autoregressive methods are hindered by costly sequential decoding, non-autoregressive models are limited by independence assumptions, and improvement heuristic solvers face issues with inference latency and learning inefficiencies in reinforcement learning frameworks. Recent progress in probabilistic generation has introduced a new class of CO solvers based on diffusion models, which have demonstrated remarkable potential in addressing NP-hard problems. Building on these AI advancements, we developed a CPD approach utilizing discrete diffusion [3] models with multinomial noise to rapidly and efficiently explore huge combinatorial sequence spaces and identify optimal solutions.

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*Speaker

Poster 03

Allosteric pocket prediction using protein language models

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Allostery is a process in which the binding of a molecule at one site on a protein induces conformational changes at a distant site, ultimately impacting protein function. Identifying the precise binding sites of allosteric modulators—known as allosteric pockets—is critical for advancing drug discovery and protein design. In this work, we tackle the classification task of predicting allosteric pockets using transfer learning with protein language models (PLMs) by developing models at both the residue and pocket levels. At the residue level, each amino acid is analyzed solely from its sequence context; however, extreme class imbalance (approximately 30 non-allosteric residues per allosteric residue) results in very low F1 scores. For pocket-level predictions, PLM-derived embeddings are combined with concise 19-feature descriptors—capturing essential physico-chemical properties of pockets identified by Fpocket—and classification is performed using feed-forward neural networks. Preliminary evaluations reveal that overall performance remains modest; while larger models (e.g., ESM3) offer some improvements, the high-dimensional final-layer embeddings are noisy compared to the concise descriptors. Perspectives include integrating information from multiple PLM layers to capture richer representations and improve generalizability, paving the way toward more accurate allosteric pocket prediction.

Keywords: Allostery, Allosteric Pocket, Protein Language Model, Transfer Learning

*Speaker

Poster 04

An Efficient Enhanced Sampling Strategy for Magnesium-Phosphate Interactions in Biological Systems

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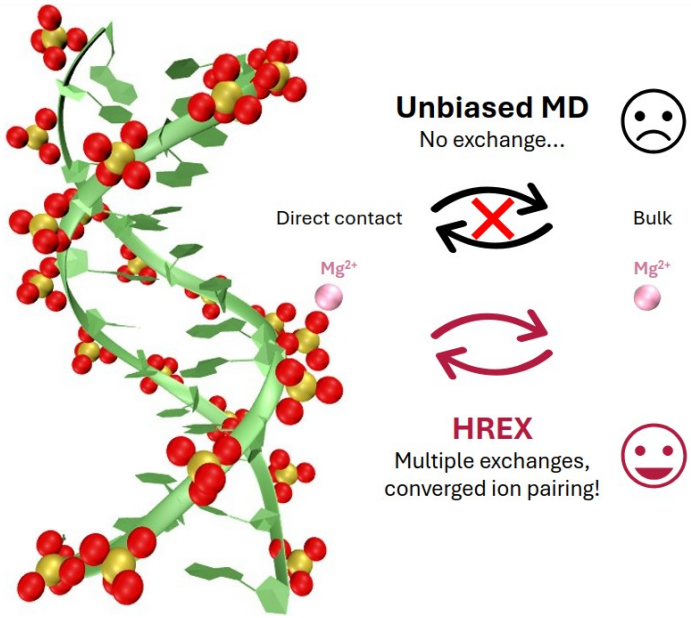

Many biological molecules contain phosphate groups, including nucleic acids and modified proteins involved in diseases like Alzheimer's. These phosphate groups are key interaction sites with ions, including divalent ions such as Mg^{2+} and Ca^{2+}. These interactions play an important role in numerous biomolecular processes, such as RNA folding.
Modeling these interactions accurately in molecular dynamics (MD) simulations comes with two major challenges: traditional force fields poorly describe these interactions, often requiring polarization effects to be included, and there are significant sampling challenges due to the extremely slow exchange ($> \mu$s) of ligands in the Mg^{2+} solvation sphere. These limitations make it difficult to properly characterize ion binding modes and sites from standard MD simulations, and limit our understanding of their impact on biomolecular structures and dynamics.

Here, we introduce an efficient and general enhanced sampling approach for studying divalent ion binding to biomolecules, demonstrated on the most challenging case of Mg^{2+} binding to phosphate-rich DNA. Our method leverages Hamiltonien Replica Exchange molecular dynamics (HREX), strategically scaling charge and van der Waals parameters across replicas to promote ion exchanges and explore different binding modes. Applied to a Dickerson's DNA dodecamer with 11 Mg^{2+} ions, our approach achieves full convergence in just 50-100 nanoseconds, whereas standard MD shows no ion exchanges, even after microseconds. It is straightforward to implement and compatible with standard MD engines capable of running Hamiltonian Replica Exchange (HREX). This efficient sampling exposes serious limitations in standard force fields which tend to overestimate binding free energies and cause ion accumulation near DNA.

*Speaker

On-going work aims to combine this strategy with HREX-based (REST2) enhanced sampling for biomolecules, opening the way for accurate simulations of complex ion-related processes, such as RNA folding with Mg^{2+}.

Keywords: Enhanced Sampling method, Magnesium-Phosphate interactions, Hamiltonian Replica Exchange, Biomolecules

Poster 05

Analysis of the interaction of cannabinoids with their human CNR1 and CNR2 receptors

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The field of hemp-derived compounds has been experiencing exponential growth, raising significant scientific, economic, and therapeutic challenges. Cannabinoids are classified into phytocannabinoids, endocannabinoids, and synthetic cannabinoids, all of which interact with various cellular targets, including the human cannabinoid receptors CNR1 and CNR2, members of the GPCR family. Among them, cannabidiol (CBD) has gained attention due to its potential effects on anxiety, pain, and inflammation. However, its interactions with these receptors remain poorly understood. In this study, we used molecular modeling approaches to explore the interaction dynamics of CBD, Δ9-tetrahydrocannabinol (THC), and tetrahydrocannabiorcol (THC7) with both CNR1 and CNR2. After completing structural data through homology modeling and energy minimization, we performed molecular docking followed by molecular dynamics simulations in a neuronal membrane environment over multiple microseconds. Several activation markers were analyzed, including ionic lock disruption, toggle switch movement, and intracellular loop (ICL3) involvement. Our results reveal complex activation dynamics. An active-like conformation of CNR1 was identified, characterized by a displacement of helix TM6 and a role of the ICL3 loop in receptor activation. Interestingly, CBD appears to facilitate access to these active states, despite its lack of classical agonist activity, suggesting a possible influence on the basal activity of CNR1. THC and THC7 exhibited distinct stabilization patterns, highlighting potential pharmacological differences. A comparative analysis of CNR2 revealed notable structural divergences in its activation pathway. These findings provide new insights into CNR1 and CNR2 activation mechanisms and may contribute to a better understanding of phytocannabinoid pharmacology, with potential therapeutic implications

Keywords: CNR1, CNR2, CBD, THC, THC7, molecular dynamics, GPCR, docking, molecular modeling, endocannabinoids, phytocannabinoids

*Speaker

Poster 06

At the center of the drug discovery universe, the chemical library software ANDROMEDA illuminates collaborative research

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In the context of early drug discovery research, effective cooperation among all the key actors – namely chemists, biologists, and in silico researchers – is crucial. However, information sharing can rapidly become challenging due to the utilization of diverse tools and media by each discipline for the storage and exchange of its primary scientific outcomes. Certain tools are specifically designed for data sharing, such as chemical library software or research suites, including the free software L-g-chimio(1), TAMIS(2) ,or the commercial software Revvity Signals(3) . Nevertheless, their usage remains constrained due to inherent limitations that restrict the capacity of specific disciplines to share their research data, offer sufficient ease of use within an entire laboratory, or in some cases, the financial burden that is difficult to assume at the academic level. To address these challenges, we introduce ANDROMEDA, an open-source chemical library software that unifies laboratory data with computational drug discovery. Developed in Python using Django(4) , PostgreSQL with the RDKit cartridge(5), and NGINX, ANDROMEDA provides a secure, local web application requiring no installation. Its intuitive interface ensures accessibility across disciplines, while Python integration enables seamless use of RDKit(5) and AI-driven prediction tools for ADMET parameters and pharmacological targets. ANDROMEDA centralizes synthesis/vendor data, biological assays, and storage information. Access is secured via IP whitelisting and user authentication, with granular permissions controlling project visibility and patentable structures. The main page displays compounds in a searchable grid, filterable by project, name, substructure, or similarity. Detailed compound pages include 1D/2D structures, physicochemical properties and structural alerts, synthesis batch data, biological activity, and supplementary files. The open-source chemical library software ANDROMEDA remains under active development and will be available on GitHub: https://github.com/cbedart/ANDROMEDA.

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Poster 07

Characterization and functional comprehension of a protein assembly: the ubiquinone metabolon from Escherichia coli.

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Surfing on the wave of Artificial Intelligence (AI) power, Alphafold2 (AF2) became a game changer for structural biology, especially for modelling macromolecular complexes. Thus, some AF2-derived methods have been developped to tackle this kind of question. Here, we aim to apply this kind of methodology to investigate a multi-enzymatic complex, called Ubi metabolon. Indeed, this supramolecular is a challenging task due to a lack of structural information and the number of protein parnters. This metabolon is composed of five enzymes (UbiE, UbiG, UbiF, UbiH, UbiI, UbiJ) and two structural proteins (ubiJ and UbiK), for which the stoichiometry is unknown. In this study, a computational framework, based on several successive steps, has been designed to model this latter. After exploring and investigating several combinations of protein interactions, our work led to the identification of a "core assembly" [1], corresponding to a subset of the biological structural organization. Finally, we think that this first 3D model could guide functional and structural characterization of the Ubi metabolon.

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*Speaker

Poster 08

Clustering data by reordering them

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The ever increasing computing power lead to MD simulations that are longer and to the extended use of enhanced sampling methods such as replica exchange. Analysis tools that are adapted to this increasing amount of data are thus needed. Clustering is a common analysis tool performed in MD simulations, but also in other areas of science such as in bioinformatics (for evolution, e.g.) or in image recognition (for CryoEM data, e.g.). Clustering is the process where data are grouped in families to either compare the sizes or dispersions of clusters, compare the properties of the clusters, or obtain representative structures. We will present a new clustering algorithm that was developped specifically for data that are noisy, such as the ones obtained from REST2 simulations. This algorithm (called YACARE) starts by reordering the data and then analyse them in an automated way. Most of the existing algorithms require input parameters which either assume that the structure of the data is known (e.g. the number of clusters) or that can't be estimated before-hand (e.g. the density of points in clusters). The YACARE algorithms uses only parameters that can be easily understood and predicted (such as the minimal size of a clusters). The algorithm was first proved to be more efficient than state-of-the-art methods on toy datasets made of normally-distributed points in a 2D space, as well as on data from REST2 simulations where the reordering approach allowed to link global and local information. We then extended the applicability of the algorithm to (i) the clustering of genes, (ii) the kinetics of a fluorescence signal, (iii) image recognition, (iv) the reduction of datasets prior to the development of neural networks potentials, (v) the clustering of chemical reactions. In all cases, YACARE is shown to be more efficient that other methods.

*Speaker

Poster 09

Coarse-grained molecular dynamics of DNA translocation through nanopores

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Nanopore experiments are an effective method for studying charged biomolecules at the single-molecule scale. A biological or artificial nanopore is inserted into a lipid or solid membrane, surrounded by an ionic solution, and an electrical potential difference is applied to drive a charged biopolymer through the pore. When a macromolecule passes through the pore, it partially blocks it and causes a decrease in the ionic current, which depends on the nature of the molecule and the properties of the pore. Alpha-hemolysin toxin is a protein nanopore widely used for this type of experiment, as it allows the passage of single-stranded DNA, making ultra-fast sequencing possible. Numerous DNA translocation and unzipping experiments have been carried out by experimentalists in our laboratory [1]. Unfortunately, these experiments do not allow access to the molecular details of the processes directly. In collaboration with experimentalists in our lab, we have chosen to study this system using molecular dynamics (MD) with a coarse-grained (CG) model. CG models are an excellent alternative to classical all-atom models, as they can provide longer and faster simulations for large systems closer to the characteristic experimental times. We first successfully achieved CG-MD simulations of the ionic transport through alpha-hemolysin, inserted into a lipid bilayer surrounded by solvent and ions, using the MARTINI CG force field and polarizable solvent, in the presence of several different electric fields to mimic the electric potential difference [2]. We validated specific features of this pore in agreement with experimental data [3]. We are now studying single-stranded DNA translocation through the protein nanopore using the MARTINI CG model. Therefore, the system composed of 500,000 atoms is reduced to 140,000 CG beads. Using steered molecular dynamics (SMD) of at least one microsecond, we simulated the translocation of several ssDNA molecules (from 10 to 19 base-long) across the pore. We studied the influence of DNA length, phosphate charges and the direction of introduction of the DNA molecule on the dynamics of DNA translocation through the nanopore. Our results show a very broad distribution of translocation times per base, in agreement with experimental results. Furthermore, we could show that the influence of the direction of introduction of the DNA molecule into the nanopore was due to a more favorable folding of the DNA bases towards the 5' end [4]. We have also studied the effects of DNA sequence and applied force intensity on translocation dynamics, proving the validity and efficiency of our coarse-grained approach.

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Poster 10

Coarse-Grained Molecular Dynamics Simulation of a VAP-A/OSBP-Mediated Membrane Contact Site

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Membrane contact sites (MCS) are subcellular regions where organelles are closely apposed (20 nm) to facilitate lipid and metabolite exchange. The endoplasmic reticulum (ER)-Golgi MCS, mediated by the interaction between VAP-A (VAMP-associated protein A) and OSBP (oxysterol-binding protein), plays a crucial role in cholesterol and PI(4)P exchange between the two compartments. However, the molecular organization and dynamic properties of this complex remain incompletely understood. Here, we used the coarse-grained (CG) Martini3 Force Field to simulate the nanoscale architecture of a VAP-A/OSBP-mediated MCS. These MD simulations are challenging because of systems sizes despite the CG use. VAP-A is incorporated into a coarse-grained lipid bilayer mimicking the ER, while OSBP associates with a Golgi-like membrane through its PH domain. The two proteins interact via the FFAT motif of OSBP, which binds to the MSP domain of VAP-A, forming the tethering complex. The simulation aims to investigate how VAP-A properties, including flexibility and density, influence membrane characteristics such as intermembrane spacing, as well as the conformational dynamics of OSBP's tethering and lipid-transfer domains. This study will provide mechanistic insights into how VAP-A and OSBP dynamics and conformation regulate MCS stability and function. Our findings will contribute to a better understanding of ER-Golgi tethering at MCS and offer a computational framework for studying other lipid transfer systems in a physiologically relevant context.

*Speaker

Poster 11

Correlation analysis of molecular dynamics reveals protein communication hotspots linked to enhanced enzymatic activity in a lactonase

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Background. Phytopathogenic bacteria are responsible for various plant diseases, leading to significant crop losses. Traditional control methods typically involve the use of copper-based or antibiotic treatments, which can be environmentally harmful, and contribute to pollution and ecosystem damage. Moreover, these bactericidal approaches promote the emergence of antimicrobial resistance. In contrast, the Quorum Quenching strategy focuses on disrupting bacterial signaling pathways, preventing the activation of virulent phenotypes without directly killing the bacteria. Within the frame of the ANR-funded Bactsqueez project, associating TBI, Gene&GreenTK and I2BC, we aim to develop robust, specific and efficient enzymatic disrupters of Quorum Sensing to fight virulence of bacterial phytopathogens. The hyperthermostable enzyme SsoPox embodies this approach, as it possesses lactonase activity and can degrade Acyl-Homoserine Lactones (AHLs), a class of signaling molecules widely used by phytopathogens for communication and virulence regulation (Elias et al., 2008). Recently, the potential of SsoPox to prevent crop losses in infected plants has been experimentally demonstrated in planta. However, its enzymatic activity can still be improved to enhance its potential for real-world applications, urging a need for further enzyme design. **Objectives**. Among the various computational strategies explored to guide the engineering of SsoPox, we describe here how molecular communication analysis can provide essential insights for enzyme design.

Methods. In this study, we conducted Molecular Dynamics (MD) simulations of the wild-type SsoPox under its functional dimeric state, along with several variants previously reported to exhibit enhanced activity. Using correlation analysis on various amino acid features in these simulations, we characterized distinct conformational states of SsoPox and the amino acids involved in both intramolecular communication and interchain communication within these states. Based on these insights, we applied a combination of rational design, coevolutionary analyses and the state-of-the-art AI software LigandMPNN to suggest relevant amino acid substitutions. These substitutions will serve as the foundation for libraries designed for high-throughput screening. **Results**. We specifically identified a loop segment located across the dimer interface that plays a crucial role in inter-chain communication, emphasizing the importance of modeling SsoPox as a dimer. This initial step allowed us to experimentally validate the discovery of two novel variants: a generalist with enhanced activity across a broad range of AHLs and a specialist with improved activity on AHL produced by Pseudomonas aeruginosa, a multi-resistant pathogen posing a serious threat to global human health. Thanks to these analyses we successfully designed a mutant library which is currently under investigation. **Conclusion**. Combining molecular dynamics simulations with correlation analysis proves to be a crucial component of enzyme design methodologies. Several SsoPox mutants with enhanced activities against several AHLs have been identified, offering new opportunities to combat the virulence of major plant pathogens.

*Speaker

Poster 12

Cross-Genotype Comparison of HEV pORF1 Domain Architecture: Insights from AlphaFold Modeling

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Hepatitis E virus (HEV) represents a significant global public health challenge, impacting approximately 20 million people annually and contributing to up to 70,000 deaths. As an RNA virus within the Hepeviridae family, HEV exhibits diverse genotypes transmitted primarily via the oro-fecal route and zoonotically. The non-structural replication polyprotein (pORF1), crucial for viral replication, comprises multiple domains, including a previously identified fatty acid-binding fold (FABD-like) domain in genotype infecting humans and swine. Notably, the presence of this domain varies across HEV species, raising questions about its functional role in viral evolution and cross-species transmission. To investigate this variability, we conducted a comprehensive molecular modeling analysis of pORF1 across different HEV genogroups. Utilizing AlphaFold, we generated structural predictions and integrated these with sequence alignment, domain annotation, and phylogenetic classification. A key aspect of our approach involved employing predicted aligned error (PAE)-based clustering to refine structural segmentation and accurately delineate domain boundaries across diverse genotypes – a critical step for comparative analysis.

Our findings reveal substantial variability in pORF1 length and domain composition among HEV genogroups. Strikingly, the FABD-like domain is uniquely present in Paslahepevirus and absent in Rocahepevirus, Chirohepevirus, Avihepevirus and Piscihepevirus. This observation suggests a potential functional specialization of the domain within human and zoonotic HEV strains. Through our work, we also demonstrate the power of AlphaFold-driven modeling to elucidate structural differences and refine our understanding of viral evolution, providing valuable insights into the functional significance of domain variability in HEV.

*Speaker

Poster 13

Des3PI: a Computational Fragment-based Approach to Design Peptides Targeting Protein-Protein Interactions

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Protein-protein interactions (PPIs) are fundamental to numerous cellular functions, and their dysregulation is frequently associated with pathological conditions [1,2]. One effective strategy for modulating PPIs involves the use of peptide-based derivatives that exhibit high binding affinity and selectivity toward their protein targets [3,4]. Peptide modulators are frequently developed by using secondary structure mimetics. However, fragment-based design has emerged as an alternative strategy in the field of PPI modulation [4]. In this context, we have developed a novel fragment-based approach, termed Des3PI (Design of Peptides targeting Protein-Protein Interactions) [5], utilizing a library composed of individual natural amino acids. Our objective is to identify the optimal sequence of cyclic peptides that can bind to a specific protein surface with high affinity. Each amino acid in the library is docked onto the target surface using Autodock Vina, followed by geometric clustering of the alpha carbons of the resulting binding modes. Within each cluster, the most frequently occurring amino acids are identified, forming the hot spots that will constitute the optimal cyclic peptide [5]. This approach have been previously applied on five protein targets involved in a PPI and show encouraging results through in silico validation which consisted in the blind redocking of all the peptides generated by Des3PI onto the protein surface and studying the stability of the resulting complexes by molecular dynamics [5,6]. However, we observed that the sequences proposed by Des3PI were often very small and aromatic amino acids were over-represented to the detriment of charged ones, which are sometimes necessary to maintain the interaction between the peptide and the protein surface and also improve their specificity. That is why we've developed Des3PI 2.0, by substantially modifying the existing approach by relying this time on the clustering of docked amino acid side chains. Des3PI 2.0 has been applied to the five systems previously studied and generates peptide sequences that are longer, more diverse and therefore potentially much more affine and specific than the first version of Des3PI. Moreover, *in silico* validation of these new peptides shows that they appear to have a stronger association with their protein target and much greater stability in molecular dynamics comparing to the peptides computed by Des3PI 1.0.

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Poster 14

Exploring molecular dynamics open data

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The surge in molecular dynamics (MD) simulation data, driven by computational advances and open science initiatives, has highlighted challenges in efficiently organizing, managing, and reusing these data. Typically stored in generalist data repositories, MD datasets become difficult to index, search, and reuse—often referred to as the "dark matter" of MD. Within the MDverse/LUMEN project, we aim to address these issues by creating a dedicated data catalogue tailored for MD simulations. This involves developing a structured database and web-based search engine using Python-based tools. Beyond datasets and file indexation, high-quality annotations and metadata is key to fostering MD data reuse. To this aim, we propose enhancing metadata and dataset annotation using Named Entity Recognition (NER). NER leverages transformer-based language models to automatically annotate datasets with key metadata such as molecule names, force fields, and software packages used. Therefore, this would significantly streamline data retrieval and promote dataset interoperability and reusability. Ultimately, this search engine hopes to represent a significant step towards transforming the "dark matter" of MD simulations into a transparent, searchable, and highly valuable resource for the scientific community.

*Speaker

Poster 15

Exploring the Conformational Dynamics of HIV-2 Protease (PR2)

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HIV-1 and HIV-2 are two etiological agents of AIDS (acquired immune deficiency syndrome). While HIV-1 is prevalent worldwide, HIV-2 remains largely confined to West Africa, infecting between 1 and 3 million people. Current antiretroviral therapies are primarily designed for HIV-1, targeting key viral proteins such as integrase, reverse transcriptase, fusion proteins, and protease (PR). The same molecules used against HIV-1 are also employed to treat HIV-2; however, some HIV-2 therapeutic targets exhibit natural resistance to these inhibitors(1–6), highlighting the need for more specific therapeutic molecules. One promising strategy involves developing inhibitors targeting HIV-2 protease (PR2), one of the four essential enzymes for viral replication. Initially, we explored the structural diversity of PR2 by characterizing and comparing the 19 available structures in the Protein Data Bank (PDB)(7). These studies highlighted regions with conserved conformations crucial for structure and function. This work enabled us to investigate the structural variability of PR2 and to identify and characterize regions capable of deforming upon ligand binding. These works led to a detailed mapping of the inhibitor binding site, identifying critical residues involved in ligand specificity(8,9). However, these studies only partially accounted for the intrinsic flexibility of PR2, which plays a crucial role in ligand binding. PR2 adopts different conformational states: the semi-open form, observed in the absence of a ligand, and the closed form, induced upon inhibitor binding(10,11). These conformations were initially identified based on crystallographic structures. To explore PR2 dynamics on a larger scale, we employed molecular dynamics (MD) simulations. We performed MD under various conditions: different starting conformations (semi-open/closed), presence or absence of a ligand, and distinct protonation states of the catalytic site (monoprotonated/unprotonated). We generated 20 simulations (0.5–1 µs each), covering eight conditions with three replicates per case. Clustering analysis of these simulations revealed novel PR2 conformations, offering new insights into its structural flexibility. These findings could aid in the design of more effective HIV-2 protease inhibitors.

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Poster 16

Exploring the impact of AI-based generative methods on peptide design by pepIT.

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Disrupting protein-protein interactions (PPIs) involved in disease is difficult with small molecules due to the large contact area of the PPI (approximately 1,000-4,000 Å) and the lack of well-defined pockets (1). Compared to small molecules, peptides have a broader and flatter interaction interface that is adapted to IPP interactions. In addition, peptide drugs offer superior stability, high purity and lower production costs (2). The search for interesting peptides or the improvement of existing peptides can be performed experimentally by biophysical approaches such as site-directed mutagenesis, by peptide shuffling or phage display techniques. However, all these experimental approaches can be time-consuming and costly. To design a therapeutic peptide able to specifically inhibit a PPI, we developed a new computational approach called PepIT (3). PepIT is an R package that implements a strategy based on binding site comparison. The method is intended to be a fast approach, usable on a large peptide bank, which could provide a pre-screening of peptide libraries. Recent advances in deep learning and generative artificial intelligence (AI) have significantly impacted complex modeling and peptide design. In particular, generative AI-based methods, such as FrameDiff (4), RFdiffusion (5), RFpeptides (6) or PepFlow (7), have significantly simplified and enhanced peptide design. Diffusion modeling generates protein backbones without relying on pre-existing designs and allows the design of peptides that bind to disease-associated proteins using only the structure or sequence of the target. In this study, we investigate: 1) whether peptides retrieved by PepIT can be significantly improved using an optimization step performed by PepFlow or RFdiffusion. 2) whether the peptides proposed by PepIT as a starting point for PepFlow or RFdiffusion can improve the peptides generated by them.

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*Speaker

Poster 17

From static to dynamic-aware macromolecular modeling

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Protein-protein interactions are fundamental to cellular processes. Identifying the interaction site is crucial to understanding protein functions and serves as the foundation for protein modeling, yet existing deep learning approaches often rely on static structures, limiting their performance when disordered or flexible regions are involved. To address this, we introduce a novel dynamic-aware method for predicting protein-protein binding sites by integrating conformational dynamics into a cooperative graph neural network (Co-GNN) architecture with a geometric transformer (GT). Our approach uniquely encodes dynamic features at both the node (atom) and edge (interaction) levels, and consider both bound and unbound states to enhance model generalization. The dynamic regulation of message passing between core and surface residues optimizes the identification of critical interactions for efficient information transfer. We trained our model on an extensive overall 1-ms molecular dynamics simulations dataset across multiple benchmarks as the gold standard and further extended it by adding generated conformations by AlphaFlow. Comprehensive evaluation on diverse independent datasets containing disordered, transient, and unbound structures showed that incorporating dynamic features in cooperative architecture significantly boosts prediction accuracy when flexibility matters, while requires substantially less amount of data than leading static models.

*Speaker

Poster 18

How Acinetobacter baumannii bacteria evade immunity? Study by analysis of transmembrane protein's interactions

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Bacterial resistance and nosocomial infections are serious threats compromising public health in numerous countries. *Acinetobacter baumannii* is an important opportunistic pathogen responsible for serious nosocomial infections and is considered one of the most threatening Gram-negative bacteria. Studies were made on *Acinetobacter baumannii* outer membrane protein OmpA interacting with fibronectin, a glycoprotein found in the extracellular matrix. The OmpA protein features a beta-barrel structure with flexible arms. These arms facilitate adherence to surfaces, colony formation, and mobility. In these studies, by using all-atom molecular dynamics simulation, the structure and the properties of the OmpA protein were analyzed. The structure of possible protein/protein complexes formed between OmpA, and the human fibronectin was also analyzed, which may ultimately lead to the immune escaping of the bacteria. For the first time, we provide plausible structure of the complex also identifying suitable amino acid mediating the interaction, and thus, constituting suitable drug targets to disrupt the complex formation.

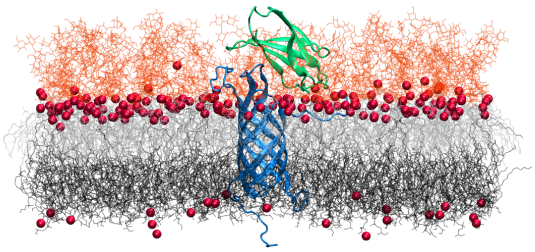

Figure: Representative snapshot of the OmpA/Fibronectin complex embedded in the *A. baumannii's* outer membrane environment. The bacterial protein is represented in blue, while the glycoprotein is shown in green. Lipids and sugars are represented in lines and Ca^{2+} ions are shown in van der Waals.

In addition, molecular dynamics simulations of the transmembrane protein revealed that water molecules could pass through the protein via the barrel, suggesting that it might also permit the passage of antibiotics. Potential of mean force were calculated with chloramphenicol, thus providing details on the technique for expelling drugs from these bacteria. These findings not only offer insights into bacterial evasion tactics but also have the potential to inform the development of novel antibacterial strategies.

Keywords: molecular dynamics, protein-protein interaction, bacteria, *Acinetobacter baumannii*

*Speaker

Poster 19

In silico design, synthesis and in vitro evaluation of peptides inhibiting protein aggregation

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With more than 55 million cases worldwide, dementia is a major global health concern often associated to the misfolding and aggregation of amyloid proteins [1]. While the exact mechanisms behind their aggregation and toxicity remain unclear, oligomers and protofibrils are believed to be the most harmful species [2]. To address this urgent medical need, strategies to prevent the aggregation processes must be developed in order to reduce the toxicity of these protein assemblies. However, targeting amyloid aggregation with small compounds can be challenging considering that it involves large and flat protein-protein interfaces. For this purpose, peptides appear to be a more effective strategy given their appropriate size and high specificity [3]. To design peptide binders, *in silico* approaches can serve as powerful tools since they offer a cost and time-efficient strategy, by exploring molecular interactions and pre-selecting promising candidates before *in vitro* validation. On this note, Des3PI, a tool using a fragment-based approach to design cyclic peptides inhibiting protein-protein interactions was developed in the group [4]. After screening an amino acid library, this method clusters the generated binding modes and identifies the most recurrent amino acids as hotspots. These hotspots are then ranked and connected to generate the best cyclic peptide sequences. Des3PI exhibited encouraging preliminary results on the amyloid β protein [4]. For this study, we applied this method, on two amyloid proteins, Aβ and Tau, both involved in Alzheimer's disease. For each protein target, the generated peptides are ranked, and the best 20 are selected for *in silico* validation with a blind docking of the peptides onto their target protein

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*Speaker

Poster 20

In silico exploration of P2RX7 opening dynamics to develop selective modulators with broad-spectrum therapeutic applications

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P2RX7 is an ATP-gated cation channel composed of three protein subunits, which is widely expressed across various cell types, with research being predominantly focused on in immune cells. Activation of P2RX7 at inflammatory sites has been shown to be deleterious, through the perpetuation of the release of inflammatory cytokines, thereby contributing to various inflammatory disorders. Consequently, a significant number of companies have initiated R&D programs to develop P2RX7 antagonists, also termed negative allosteric antagonists (NAM). However, the activation of P2RX7 may also have beneficial effects in the defence against intracellular pathogens and cancerous cells, and there is a need for good pharmacological drugs acting as positive allosteric modulators (PAM) of P2RX7. The exploration of the dynamics of the P2RX7 structure in close proximity to a potent yet stereoselective antagonist (AZ11645373) has enabled the mapping of stereospecific intermolecular interactions with the active (R)-enantiomer within the allosteric extracellular site. These interactions form a network that prevents the coordinated conformational transition of the three extracellular domains, thereby preventing the opening of the transmembrane channel 3. The dynamics of the P2RX7 structure in the vicinity of the active state bound to ATP have been shown to contain a highly probable binding site, in line with published data of site-directed mutagenesis experiments, for the only known but highly cytotoxic CK-ginsenoside PAM. It has been demonstrated that classical MD dynamics simulations are sufficient to show conformational transitions of transmembrane helices, leading to successive opening and closure of the channel by a lock composed by the Ser342 residue of the three chains, irrespective of the state of the structure. However, a more in-depth investigation into the free energy landscape between these sampled, contrasted states will be conducted by metadynamics coupled to induced-fit docking of PAM hits. These discoveries are intended to be used to identify new drug-like and non-toxic modulators capable of boosting P2RX7 efficacy.

*Speaker

Poster 21

Investigating RNA Local Geometry: Conformational Effects of SHAPE Reagent Reactions

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RNA structure plays a fundamental role in its function, influencing processes such as catalysis, recognition, and regulation. Chemical probing techniques like Selective 2'-Hydroxyl Acylation analyzed by Primer Extension (SHAPE) provide valuable insights into RNA structure by modifying flexible nucleotides and revealing their reactivity(1). However, SHAPE reactivity is typically interpreted as an individual nucleotide property, without fully accounting for potential conformational changes in neighboring nucleotides. It was observed that when a SHAPE reagent reacts with a specific nucleotide, the conformations of adjacent nucleotides are also affected during the reaction process (2-3). This study aims to investigate these local structural modifications and their implications for RNA dynamics. To explore this phenomenon, we use standard and enhanced molecular dynamics (MD) simulations to model RNA structural fluctuations before, during, and after SHAPE modification. By capturing detailed atomic-level motions, we aim to characterize how local nucleotide conformations shift in response to SHAPE-induced modifications. While other structural descriptors such as accessible surface area (ASA) are often used in SHAPE analysis, our study seeks to move beyond ASA by identifying additional geometric features that contribute to nucleotide flexibility and reactivity. This involves analyzing local structural parameters such as torsional angles, hydrogen bonding patterns, and stacking interactions and their combination providing a more nuanced understanding of RNA conformational behavior. By investigating how SHAPE modifications influence local RNA geometry, this work aims to refine the interpretation of SHAPE data and improve our understanding of RNA structural dynamics.

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*Speaker

Poster 22

Light-controlled modulation of TIM-3 immune response via photoswitchable lipids

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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 lipids1. 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 signaling2. 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.

*Speaker

Poster 23

Martini Cocktails: Mixing topologies for relative coarse-grained free energy calculations

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The Martini force field, originally conceived for studying lipid membranes with coarse-grained resolution, is being increasingly adapted towards molecular design and biotechnological applications [1-3]. Recently Martini has proven its capacity to predict protein-ligand binding affinities based on unbiased MD simulations with no a priori knowledge of the binding site [4-5]. The latter opens the perspective of developing highly efficient pipelines for drug discovery based on coarse-grained simulations [6]. Traditional hit-to-lead pipelines often employ relative binding free-energy (RBFE) calculations based on alchemical transformations. This area remains to be explored in Martini, as there are no benchmarks, guidelines, or dedicated codes to facilitate such calculations. In this work, we take a step toward overcoming these limitations, demonstrating how mixed-topology approaches can be implemented within Martini. This is exemplified by generating small-molecule Martini topologies containing alchemical beads that are able to transition between two states , and using them to explore partitioning equilibria via non-equilibrium FEP simulations. The results show that mixing topologies in Martini (Martini cocktails) offers great promise for the efficient quantification of relative free energy changes in chemical equilibria.

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*Speaker

Poster 24

Mechanism of Ag+-induced folding of a bacterial peptide from molecular dynamics simulations

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Interactions between proteins and metal cations are central to biochemical processes and shape protein structures and conformational landscapes. Unlike other metal cations, Ag+ and its interaction with proteins are not well studied. Yet, Ag+ has antibacterial properties and is used in a variety of treatments, against which bacterial resistance is emerging. It is important to understand the molecular bases for bacterial Ag+ resistance, notably by describing the structural consequences of Ag+ binding to silver resistance proteins. Among these latter, SilE is intrinsically disordered in the absence of silver, and locally folds into α-helical segments upon Ag+-binding. The atomic details of this silver-induced folding, and its significance for bacterial resistance to silver, are still unclear. Focusing on the 11-residue B1 peptide fragment from SilE, we investigate here the mechanism of Ag+-induced folding into an α-helix using molecular simulations, NMR, and deep learning. First, we parametrize a bonded model of Ag+-protein interactions for CHARMM36m using DFT calculations. Then, we perform extensive temperature replica-exchange MD simulations of B1 in the absence and the presence of bound Ag+ (78 μs aggregate time). We reweight the trajectories with MBAR and compute free energy landscapes along bespoke collective variables, including latent variables learnt with an autoencoder neural network. Further, we implement a string method-based strategy to extract minimum free energy folding paths from the trajectories. This enables us to elucidate B1's folding landscape and how it is shaped by Ag+. In agreement with experiments, we find that B1 is mostly unfolded in the absence of Ag+, whose binding to B1 shifts the equilibrium toward the α-helical form. We then characterize the folding pathways of B1, observing that Ag+ alters the folding mechanism by stabilizing different intermediates as compared to when Ag+ is absent. The autoencoder reveals additional metastable conformers that do not lie on the folding pathways. The centrally positioned E6 residue appears critical for stabilizing the helical form, a hypothesis we test by characterizing the B1 E6Q mutant by NMR and simulations. Both consistently show that this mutant has a decreased tendency to fold into an α-helix even in the presence of Ag+. Overall, we describe an original case of metal-induced folding and set the stage for the computational investigation of the full-length SilE IDP, opening the way to atomically detailed insights into the mechanisms of bacterial silver resistance.

*Speaker

Poster 25

Mfd a revolutionary target to combat antimicrobial-resistance

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In the context of rising antimicrobial resistance (AMR), the urgent search for new antimicrobials led us to identify Mfd, a bacterial protein, as an innovative target for drug development (WO/2017/191184). Mfd plays a key role in bacterial virulence and grants resistance to nitric oxide, a crucial antimicrobial defense mechanism—by promoting the repair of NO-induced DNA damage 1-3. Mfd, a non-essential transcription-repair coupling factor found exclusively in bacteria, recognizes RNA polymerase stalled at non-coding lesions4. It hydrolyzes ATP to dismantle the transcription complex, and to recruit components of the nucleotide excision repair machinery. Mfd promotes mutations, thereby accelerating the development of antibiotic resistance 5. A high-throughput in silico screening was conducted to identify molecules that specifically bind to Mfd's active site. The molecular mode of action was characterized in E. coli and extended to the ESKAPE group of pathogens, priority targets in AMR. The identified compounds demonstrated in vitro efficacy and in vivo non-toxicity when tested in an insect infection model for two pathogens. Subsequently, an optimal inhibitor scaffold was refined, with derivatives currently undergoing in vitro and in vivo optimization6. To fulfill its various functions, Mfd undergoes significant structural remodeling to interact timely and spatially with its cognate partners, namely RNA polymerase and NER proteins. This structure-function cycle, previously elucidated using cryo-electron microscopy, was explored through molecular dynamics simulations. These studies revealed that the linkers connecting Mfd's functional modules and partially disordered segments are neither spacers nor structural connectors. Instead, they exhibit intrinsic properties that mediate disorder-to-coil transitions, enabling the dynamic reshuffling of Mfd's functional machinery. I look forward to discussing how Mfd represents a promising prototype for designing novel antimicrobial strategies, expanding our arsenal in the fight against the AMR.

*Speaker

Poster 26

Modeling the interaction between the silver(I) ion and proteins with 12-6 Lennard-Jones potential: a bottom-up parameterization approach

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Silver(I) ions and organometallic complexes thereof are well established antimicrobial agents. They have been employed in medical applications for centuries. It is also known that some bacteria can resist to silver(I) treatments through an efflux mechanism [1]. However, the exact mechanism of action remains unclear. All-atom force-field simulations can provide valuable structural and thermodynamic insights on the molecular processes of the underlying mechanism. Lennard-Jones parameters of silver(I) have been available for quite some time [2]; their applicability to describe properly the binding properties (affinity, binding distance) between silver(I) and peptide-based binding motifs is, however, still an open question. Here, we demonstrate that the standard 12-6 Lennard-Jones parameters (previously developed to describe the hydration free energy with the TIP3P water model [3]) significantly underestimate the interaction strength between silver(I) and both methionine and histidine. These are two key amino-acid residues in silver(I)-binding motifs of proteins involved in the efflux process [4]. Using free-energy calculations, we calibrated NBFIX parameters for the CHARMM36m force field to reproduce the experimental binding constant between amino acid sidechain fragments and silver(I) ions [5]. We then successfully validated the new parameters on a set of small silver-binding peptides with experimentally known binding constants [6]. In addition, we could monitor how silver(I) ions increase the alpha-helical content of the B1b oligopeptide, in agreement with previously reported Circular Dichroism (CD) experiments [7]. When applied to the SilF protein, our simulations were capable to identify not only the binding site of silver(I) ion but also the correct coordination geometry as seen by NMR studies [8]. Future improvements are outlined. The implementation of these new parameters is straightforward in all simulation packages that can use the CHARMM36m force field. It sets the stage for the modeling community to study more complex silver(I)-binding processes such as the interaction with silver(I)-binding transporter proteins.

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Poster 27

Molecular Bases and Specificity behind the Activation of the Immune System OAS/RNAse L Pathway by Viral RNA

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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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*Speaker

Poster 28

Molecular modeling of the intrinsically disordered protein oligomers TDP43 interacting with RNA GU12

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TAR DNA binding protein 43 (TDP43) is a versatile RNA/DNA binding protein involved in RNA-related metabolism (1). TDP43 has several intrinsically disordered regions lacking of stable secondary or tertiary structures including four primary domains: an N-terminal domain (NTD) and two RNA-recognition motifs (RRM1 and RRM2), all of which are well-structured, and a highly disordered C-terminal low-complexity domain (LCD) (2). The accumulation of TDP43 aggregates in the central nervous system is a common feature of several neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), alzheimer's disease (AD) and limbic predominant age-related TDP43 encephalopathy (LATE), however, the exact mechanisms mediating the formation of TDP43 aggregates remain elusive (3). Previous experimental studies showed the affinity of the two RRMs to GU-rich RNA sequences (4), and their blocking effect on the TDP43 aggregation (5). Unfortunately, the molecular details of this RNA binding mechanism and its aggregation-preventing effect remains undiscovered since traditional experimental methods such as X-ray or NMR are unsuccessful to investigate the conformation of such intrinsically disordered proteins. To fill this gap, we employed all-atom molecular dynamics (MD) simulations to study the conformation of TDP43 with its interactive RNA. We performed all-atom MD simulations on TDP43 alone (NTD-RRM12), TDP43 (NTD-RRM12) monomer/GU6 complex and TDP43 (NTD-RRM12) dimer/GU12 complex independently, using the AMBER03ws (6) and the AMBERchiol3 (7) force fields for protein and RNA respectively. We then compared the simulation data with the available experimental Small-angle X-ray scattering (SAXS) data based on CRYSTOL 3.0 (8). According to the preliminary results of our study, we observed that the AMBER03ws and AMBERchiol3 force fields are appropriate for simulating the TDP43 alone and the TDP43/RNA complex. In order to improve our understanding of our MD simulations, we applied GAJOE (9, 10) to select structures that are in good agreement with experimental SAXS data for each system, through calculating radius of gyration, a measure of compactness. Additionally, we calculated the RMSD of each domain and the minimum distance between each domain, to evaluate the effect of RNA interaction with the TDP43.

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Poster 29

MolPlay: Interactive Molecular Simulations and Analyses for Everyone

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Interactive molecular simulations and analysis (IMSA) provide powerful tools for real-time molecular exploration, but their uptake remains limited due to technical complexity and limited resources. MolPlay was developed to overcome these obstacles by providing a portable plug-and-play platform for IMSA. MolPlay is a USB-based solution that integrates pre-configured molecular simulation and visualization tools, including UnityMol for real-time interaction and MDDriver for dynamic simulations. Users can explore molecular systems without complex installations, making advanced simulations accessible to researchers, teachers and students alike. It comprises examples to **Manipulate**, **Explore** and **Analyze** for a range of applications from membrane and protein dynamics to drug discovery and materials science. The platform simplifies the setup of simulations, interactive modeling and real-time analysis, opening up new possibilities for molecular research and education. With MolPlay, we are introducing a new paradigm for interactive molecular simulations and making high-quality computational tools more accessible than ever.

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*Speaker

Poster 30

Naive prediction of complete protein complex structure using AlphaFold, applied in Type 4 secretion system

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Bacteria employ various secretion systems to interact with other organisms. The Type 4 Secretion System (T4SS) is particularly significant due to its conservation across bacterial species and its involvement in essential biological processes. This system can secrete DNA, facilitating inter-bacterial genetic exchange and thus contributing to the transfer of resistance genes. It can also secrete proteins, many of which are toxic to eucaryotic cells. Artificial intelligence and structural model prediction, recognized with the 2024 Nobel Prize in Physics, have demonstrated exceptional ingenuity and precision. These advancements are proving to be effective in predicting protein-protein interactions (PPIs). Here, we developed an automated pipeline to predict large sets of PPIs. Applying this method to T4SS plasmids enabled us to identify novel homologous proteins, even in the absence of sequence or structural homology. Furthermore, this approach provides a foundational perspective on the T4SS, allowing us to propose robust hypotheses about its assembly.

*Speaker

Poster 31

Optimizing Odorant Receptor Stability and Expression

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Despite belonging to the well-studied class A of GPCRs, knowledge about Odorant Receptors (ORs) remains limited due to the complexity of their study. Among the 400 members of the human OR family, only a few are efficiently expressed on the surface of common cell line models, leading to a poor understanding of their mechanisms and pharmacological behavior. In this project, we hypothesize that ORs lack cell surface expression due to the poor stability of their structure in the membrane of cell models. We aim to enhance OR cell surface expression by modifying their amino acid sequences, allowing us to better understand the role of each residue in OR structure stabilization. These modifications are guided by *in silico* prediction methods and validated *in vitro* through site-directed mutagenesis and flow cytometry providing feedback to our *in silico* methods. This project could pave the way for developing a machine-learning model capable of decoding the elements of the 400 OR sequences driving their stability and expression. Beyond sequence modifications, this work contributes to the elucidation of OR structures, their purification, activation tests, and broader biological investigations. This research serves as a gateway to unraveling the mysteries of olfaction.

*Speaker

Poster 32

Robust conformational space exploration of cyclic peptides by combining different MD protocols and force fields

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Cyclic peptides are an important class of pharmaceutical drugs. We used here replica-exchange molecular dynamics (REMD) and simulated tempering (ST) simulations to explore the conformational landscape of a set of nine cyclic peptides. The N-ter to C-ter backbone cyclized peptides of seven to ten residues were previously designed for a high conformational stability with a mixture of L and D amino acids. Their experimental NMR structures were available in the protein data bank (PDB). For each peptide we tested several force fields, Amber96, Amber14, RSFF2C and Charmm36 in implicit and explicit solvent. We find that the variability of the free energy maps obtained from several protocols is larger than the variability obtained by just repeating the same protocol. Running multiple protocols is therefore important for the convergence assessment of REMD or ST simulations. The majority of the free energy maps showed clusters with a high RMSD to the native structures, revealing the residual flexibility of this set of cyclic peptides. The high RMSD clusters had in some cases the lowest free energy, rendering the prediction of the native structure more difficult with a single protocol. Fortunately, the combination of four implicit solvent REMD and ST simulations, mixing the Amber96 and Amber14 force fields, predicted robustly the native structure. As implicit solvent in the REMD or ST setup are up to one hundred times faster than explicit solvent simulations, so running four implicit solvent simulations is a good practical choice. We checked that the use of an explicit solvent REMD or ST simulation, taken alone or combined with implicit solvent simulations, did not significantly improved our results. It results that our combination of four implicit solvent simulations is tied in terms of success rate with much more expensive combinations that include explicit solvent simulations. This may be used as guideline for further studies of cyclic peptide conformations.

*Speaker

Poster 33

Role of AIF intrinsically disordered C-loop in regulating CHCHD4 binding

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Protein-protein interactions (PPI) play a crucial role in many physiological and pathological processes in cells. They often involve intrinsically disordered proteins (IDP) and intrinsically disordered regions (IDR), which are abundant in the eukaryotic proteome. IDP/IDRs functions are essential for cell signaling, regulation and cycle, despite the lack of a single and stable three-dimensional structure. In particular, the interaction between the apoptosis inducing factor (AIF) and the N-terminal of coiled-coil-helix-coiled-coil-helix domain containing 4 (CHCHD4) is required for an optimal functioning of the respiratory chain mechanism, cell proliferation and survival. Inhibiting the AIF/CHCHD4 interaction in cancer cells, could represent a new therapeutic strategy.

The AIF/CHCHD4 interaction involves dynamic and disordered regions which undergo large conformational rearrangements upon binding with ligands, presumably allowing the interaction with CHCHD4. However, the dynamics and allosteric mechanisms are not completely understood. Although AlphaFold can be used to model one conformation of the complex, the second experimentally known conformation seems to be missing. With the aim to pave the road to novel therapeutical developments, molecular dynamics simulations are here used in combination with AlphaFold predictions to decipher the path between the two conformations, the role of ligands, the allosteric mechanisms, and the interaction with CHCHD4, in this crucial complex.

*Speaker

Poster 34

Simulated Solute Tempering 2

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Efficient exploration of protein conformational space is essential for elucidating the dynamics and functional mechanisms of biological macromolecules. To this end, we present the simulated solvent tempering version 2 (SST2) algorithm, which synergistically integrates the strengths of simulated tempering (ST) and replica exchange solvent tempering 2 (REST2), aiming to enhance sampling efficiency while maintaining practical ease of implementation. In this study, we rigorously evaluate the performance of SST2 by benchmarking it against both the established ST algorithm and REST2. We apply these algorithms to two prototypical toy systems: the chignolin peptide (CLN025) and the miniprotein Trp-Cage. Utilizing extensive molecular dynamics (MD) simulations, we achieve an aggregate simulation time scale reaching the millisecond range, unprecedented in scope. Our findings reveal that SST2, akin to REST2 simulations, effectively reconstructs the thermal stability profiles of the simulated peptides. While SST2 demonstrates comparable performance to ST and REST2 in sampling conformational space, it does not exceed it under standard conditions. However, we illustrate that by elevating the reference temperature, SST2 can surpass ST and REST2 in terms of efficiency. Furthermore, SST2 simulations of the protein-peptide complex p97/PNGase underscore the algorithm's exceptional sampling efficiency in ligand binding events, highlighting its potential for investigating protein-ligand interactions and providing novel insights into molecular recognition processes. The comparative analysis with REST2 further substantiates SST2's efficacy and versatility in computational biophysics research.

*Speaker

Poster 35

Specific binding modes of SIRT6 C-terminal domain to the nucleosome core particle promote DNA unwrapping and lysine accessibility

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Sirtuins are a class of NAD-dependent histone deacetylases that regulate important biological pathways in prokaryotes and eukaryotes. This enzyme family comprises seven members, named SIRT1 to SIRT7. Among them, Sirtuin 6 (SIRT6) is a human sirtuin that deacetylates histone H3 and plays a key role in DNA repair, telomere maintenance, carbohydrate and lipid metabolism, and lifespan. SIRT6's structure consists of a zinc finger domain, a Rossmann fold domain containing the NAD+ binding site, and disordered N-terminal and C-terminal (CTD) extensions. The specific role of the CTD on SIRT6 interaction with nucleosomes for histone deacetylation remains unclear. Here, we resort to extended molecular dynamics simulations to uncover the dynamical behavior of the full-length SIRT6 bound to a nucleosome core particle. Our simulations reveal that the CTD preferentially interacts with DNA at the entry/exit point near the enzyme's docking site, exhibiting a variety of different binding modes. In specific cases, the CTD participates to the promotion of DNA unwrapping, also modulating the accessibility of target lysine residues located near the H3 histone core to SIRT6's active site. This work provides new structural insights into the binding process of the full-length SIRT6 to a nucleosome core particle, highlighting its participation in DNA unwrapping and lysine accessibility promotion.

*Speaker

Poster 36

Staphylococcus aureus ribosome in trans-translation as a target for novel antibiotic design

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The development of antibiotic-resistant microorganisms is one of the major public health issues of our century. In this context, the present project is to design antimicrobial molecules aimed at a new target: bacterial trans-translation. Trans-translation refers to a molecular process which allows for the release of ribosomes stalled on faulty mRNAs that lack stop codons as well as the elimination of these mRNAs and mistranslated peptides. The process is performed by the hybrid transfer-messenger RNA (tmRNA) and a small basic protein (SmpB). Essential for the survival and/or virulence of many pathogenic bacteria, and absent in eukaryotes, trans-translation is a particularly attractive targets for new antibiotics. We presently solved by cryo-EM the structure of *Staphylococcus aureus* ribosome in the trans-translation state. Starting from the cryo-EM model, we used Virtual Flow protocol to screened Enamine Real chemical library to propose new inhibitors of the SmpB–tmRNA interaction. In the mean time we developped a RFdiffusion-based method to design peptide binder targeting protein-RNA interface on SmpB.

*Speaker

Poster 37

Stapled peptides: a new strategy to design innovative selective inhibitors to disrupt LIMKs-cofilin interaction

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LIM Kinase family comprises only two members: LIM kinase 1 (LIMK1) and LIM kinase 2 (LIMK2).(1) Known as dual kinases, LIMKs phosphorylate serine/threonine and tyrosine residues. They are pivotal key regulators of cytoskeleton remodelling and implicated in actin filament and microtubule dynamics. They are thus involved in other biological processes such as cell motility, morphogenesis, division, apoptosis, neuronal morphology and neuritogenesis.(2) Many proteins are regulated by LIM kinases, among them cofilin which is inhibited when phosphorylated; leading to the suppression of actin filament depolymerisation. Actin turnover is an essential process for cell shape, motility, division and intracellular transport.(3) Consequently, LIM kinases are highly associated with various pathologies like cancers, ocular diseases, neurofibromatosis types I, II and neural diseases.(2,4) Up till now, to target cytoskeleton remodelling, two main strategies were implemented. The first one has extensively targeted microtubule turnover by small molecules often leading to side effects and chemoresistance. For the second one, it acts on actin filament turnover. Many small molecules were then designed to inhibit LIMK activity, however only one molecule, LX7101, reached phase II clinical trials for glaucoma with no further published results.(5) Resolved crystallographic structures in protein data bank (PDB ID: 5HVK, 5L6W) deciphering LIMK1-cofilin interaction have revealed that the binding occurs between the α-helix 5 of cofilin and the accommodated corresponding groove of LIMKs.(6,7) As the binding interface is distal from the active site used by the kinase to phosphorylate Ser3 residue of cofilin, a promising approach is to selectively disrupt the protein-protein interaction without inhibiting the phosphorylation of all unrelated other substrates to avoid off-targets side effects. In this project, we aim to inhibit the LIMK-cofilin interaction by designing short-stapled cyclic peptides. The cross-link (staple) between the side chains of 2 amino acids is capable of retaining a helical conformation of peptides similar to that of cofilin. Such approach is also interesting to enhance the affinity of these molecules, to confer protease resistance and to increase cell permeability.

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Poster 38

Strange, a pharmacophore-based approach for molecular interaction

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Molecular interaction analysis plays a critical role in drug discovery, structural biology, and molecular modelling. For instance, during molecule docking, interaction analysis enables discrimination between true and false positives by identifying relevant interactions between the ligand and the binding site. A better understanding of the ligand-target interaction can give the user important insights into possible hit-to-lead optimization strategies.

Currently, multiple open-source software packages are used for interaction analysis, such as PLIP (1,2). However, the latter has several limitations: limited support for non-biological molecules, unable to process all the wide variety of input file formats, and problems with dependencies.

Here, we introduce strange, a new python package, to get around these limitations. It uses pharmacophores to detect possible interaction sites, thus making it independent of ligand or receptor type. This generalization means that strange natively supports a wide array of molecules and biomolecules such as DNA, RNA, and other polymers. This flexibility will simplify the design of post-processing workflows for filtering hits in docking experiments. Furthermore, strange will support in the future interaction analysis for molecular simulations. Thus enabling for instance the analysis of interaction between lipids and proteins.

In addition, strange leverages two popular open-source packages, MDAnalysis and RDKit, to perform interaction analysis. Both packages have Long Term Support. It enables the package to parse more file formats (mol2, mol, pdb, gro, etc.). To finish, the tool outputs interaction data in .csv format for easy readability and storage for further analysis.

With its speed, versatility, and pharmacophore-based design, strange aims to become a resource for molecular interaction analysis, bridging computational efficiency with broad applicability.

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*Speaker

Poster 39

Structure-guided design of small-molecule agonists for neurotensin receptors identifies nonopioid analgesics

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Peptide-activated G protein-coupled receptors play crucial roles in numerous diseases, but remain difficult therapeutic targets due to the challenges in developing small-molecule drugs. We explored strategies to identify small-molecule agonists for the neurotensin (NTS) peptide receptors, which hold promise for the development of safer pain medications. Chemical libraries of drug-like molecules were first designed based on a receptor-peptide complex, and then 14.5 million compounds were computationally docked to the orthosteric binding site of the NTS1 receptor. A set of 39 top-ranked compounds were synthesized, and seven of these were experimentally confirmed to activate the NTS1 receptor. Structure-guided optimization yielded submicromolar and crystal structures of these compounds in complex with the NTS1 receptor confirmed the predicted ligand-binding modes and provided insights into the molecular basis of pathway-specific activation. One ligand exhibited nanomolar affinity for the human NTS2 receptor and antinociceptive activity in a rodent model, providing a starting point for the development of non-opioid analgesics. To enable the use of our virtual screening approach for other peptide-binding drug targets, we share tailored chemical libraries containing billions of readily synthesizable compounds.

*Speaker

Poster 40

Study of conformational changes in biliverdin within the phytochrome using hybrid all-atom/coarse-grained simulations

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Phytochromes are a large family of photoreceptor proteins composed of two domains: PAS (Per-ARNT-Sim) and GAF (cGMP-phosphodiesterase/adenylate cyclase/FhIA [1]. The PAS domain binds a linear tetrapyrrole chromophore via a cysteine residue. The biliverdin chromophore, a bile pigment derived from the breakdown of the heme [2], is present in various organisms. Biliverdin absorbs and emits light in a specific range, making it important in the study of light-sensitive proteins and their applications in biotechnology and medicine. A deeper understanding of this system will offer valuable insights for designing new devices that emit red-colored photons, thereby producing light signals that are more easily detectable within the human body [3].

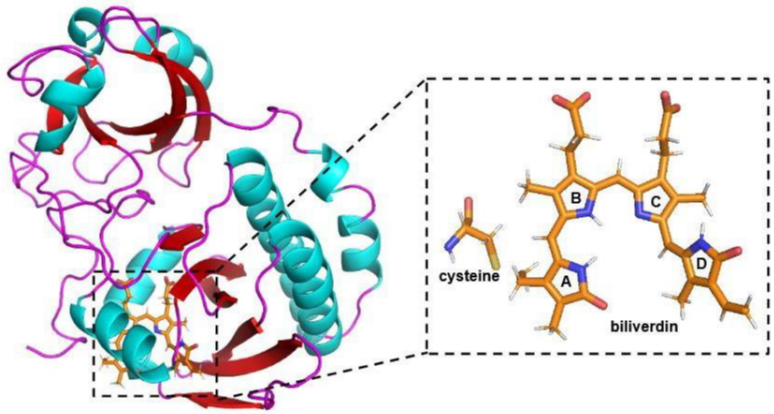

Figure 1: Representation of the biliverdin within the protein.

In this research, we aim to construct the energy profile that connects two protein structures including biliverdin in two distinct conformations: compacted and extended, which absorb at different wavelength. This analysis is important for understanding the molecular mechanisms behind conformational changes in phytochromes. For that, we performed umbrella sampling [4] simulations with hybrid AA/CG (All-Atom/Coarse-Grained) representation using SIRAH force field [5] for the coarse-grained part and homemade force field for the all-atom part. The energy profile provides us information on the feasibility of the conformational transition, revealing key factors that govern this process. Additionally, molecular dynamics simulations allow us to analyse the trajectories of the protein over time, offering a detailed view of how interactions between the protein and biliverdin stabilize one conformation over another. By identifying the driving process behind the conformation transitions, we can better understand how phytochromes function and the way for future applications in designing light-sensitive biomolecular tools.

Keywords: phytochromes, umbrella sampling, hybrid AA/CG, biliverdin, molecular dynamics

*Speaker

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Poster 41

Targeting the DC-SIGN Tetramer for Photodynamic Therapy

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Photodynamic therapy (PDT) has been developed in recent years as a less damaging way to treat tumors. A photoreactive agent (Photosensitizer, PS) is internalized by the tumor cell, where it will be activated by light and produce reactive oxidative species (ROS), destroying the tumor cell from the inside. The challenge remains to target only the tumor cells, and not the surrounding tissues. By linking the PS to mannose, we target the by tumor cells highly expressed mannose receptor DC-SIGN. At the same time, binding to the mannose receptor MRC1 expressed by the surrounding cells needs to be avoided. By doing MD simulations of both the DC-SIGN tetramer and the MRC1 multi-domain receptor in combination with the sugar-linked PS, we try to solve this issue in a 3D-structure based fashion.

*Speaker

Poster 42

Targeting the RIPK2/XIAP-BIR2 Interaction: A Molecular Modeling Strategy for Inflammation Modulation.

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The X-chromosome-linked inhibitor of apoptosis protein (XIAP) plays a crucial role in regulating apoptosis and immune responses, particularly by modulating the NOD2 signalling pathway. This pathway is overactivated in inflammatory diseases such as Crohn's disease and sarcoidosis, making XIAP a promising therapeutic target. The interaction between XIAP and serine/threonine/tyrosine-protein kinase 2 (RIPK2), mediated via the BIR2 domain of XIAP, is essential for RIPK2 ubiquitination and the subsequent production of pro-inflammatory cytokines. Disrupting this interaction with small-molecule inhibitors presents a novel strategy for selectively modulating inflammation. In this study, we will employ molecular modeling techniques to optimize small molecules that selectively target the XIAP-BIR2 domain. To achieve this, molecular dynamics simulations will be conducted on the RIPK2/XIAP-BIR2 complex, resolved using cryo-EM, and combined with binding free energy calculations to identify key interactions between RIPK2 and XIAP-BIR2 that are potential targets for disruption. These findings will serve as a foundation for the pharmacomodulation of initial hit compounds. The newly designed inhibitors, validated through in silico studies, will then be synthesized and evaluated in vitro to assess their affinities for the XIAP-BIR2 domain, by a test using alphascreen technology.

*Speaker

Poster 43

Unraveling the Calcium-Dependent Allosteric Activation Mechanism of EndoU Ribonuclease

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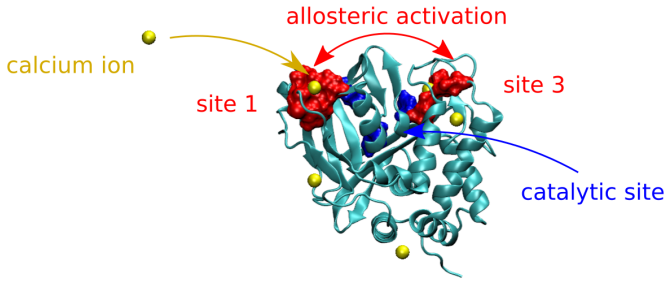
EndoU is a ribonuclease found both in bacteria and eukaryotes, recognized as a biomarker in several cancers and a potential therapeutic target. Interestingly, its activity is regulated, in eukaryotes, by Ca^{2+} ions. Recently, S.Campagne's experimental team in Bordeaux, which whom we collaborate, used a combination of several biochemical experiments to suggest a molecular mechanism for this Ca^{2+} triggered activation [1]. They evidenced a change in EndoU conformation upon Ca2+ binding and identified several binding sites for Ca^{2+} , whose importance was confirmed by mutation experiments. Overall, these experiments suggest a Ca^{2+} -dependent allosteric activation of EndoU, whose molecular details remain to be fully understood. Using molecular dynamics simulations of both the Ca^{2+} -bound and apo EndoU enzyme, isolated or in complex with an RNA substrate, we aim to uncover the molecular details of this Ca^{2+} -dependent allosteric behavior. Specific analysis strategies to characterize the Ca^{2+} -induced rearrangement pathways are implemented and combined with state-of-the-art force fields for ions. Given the high flexibility of the EndoU-RNA complex, enhanced sampling techniques will also be used to properly characterize the conformational ensemble of the complex in different conditions.



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Keywords: Allostery, RNase, Ca2+ Ions, All-atom MD, Enhanced Sampling

*Speaker

Poster 44

Interaction of Apis Mellifera nicotinic Acetylcholine Receptors with Acetylcholine: New Insights from Docking and Molecular Dynamics Simulations

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Apis mellifera (*Am*) bees, the main pollinating insects, are crucial to agriculture. They are under threat from the use of neonicotinoid insecticides.(1) These molecules act as agonists of nicotinic acetylcholine (ACh) receptors (nAChRs), pentameric transmembrane receptors responsible for signal transmission in the nervous system. Ligand binding occurs in the extracellular domain at the interface between two subunits, in an interaction pocket consisting of three loops from the main subunit (A, B, C) and three loops from the complementary one (D, E, F).(2) In vertebrates, it has been shown that heteromeric nAChRs like a4b2 exist in two main stoichiometries ((a4)2(b2)3 and (a4)3(b2)2) with specific electrophysiological and binding properties.(3) Numerous subunits of the nAChRs in honeybees have been sequenced.(4) However, their three dimensional experimental structures are inexistent. In this context, experimental structures of the Acetylcholine (ACh) Binding Protein (AChBP), recognized as a surrogate of the ligand binding domain (LBD) of nAChRs, provide relevant alternatives. Our project, which takes place in the context of a collaboration with electrophysiologists that have been able to measure ionic currents of various heteromeric bees nAChRs (αn)x-(β2)y (with n=2,3,4; x,y=2,3 or x,y=3,2) in presence of agonists, has for objective to understand at the atomic level, through molecular modelling methods, the toxicity of neonicotinoids for *Am* bees.

The first step of the present study was to model the different extracellular domains of (αn)x-(β2)y*Am* nAChRs in both stoichiometries using established homology modelling programs, AlphaFold and SWISS-MODEL. In a second step, molecular docking studies of ACh with the different modelled isotypes of nAChRs LBDs selected have been carried out with the Autodock-Vina program using a semi rigid protocol. Molecular dynamics (MD) simulations were thereafter realised to investigate the behavior of the different complexes obtained from the docking with the ACh ligand as a function of time. For this study, the CHARMM force field, for which parameters are available for ACh, has been used with NAMD. 5 replicas of 500 ns simulation time were produced for each nAChR LBD-ACh complex. Our study allows, for our reference ligand ACh, to (i) highlight the relative importance of the various (αn)x-(β2)y loops in the binding; (ii) determine the interactions established in the orthosteric site at the two interfaces (α/α and α/β) for the different isotypes; (iii) describe the stability of ACh in the different sites through time and the relative flexibility of the corresponding loops. From the first results we have obtained, ACh appears more stabilized in the α/α interface compared to the α/β one, whatever the nature of the subunit. The molecular modelling protocol used allows to bring to light, at the atomic level, the key interactions of ACh with the different nAChRs isotypes considered. The same strategy will be applied to other ligands of *Am* nAChRs, such as nicotine and insecticides acting as competitive modulators of *Am* nAChRs. On the whole, our work will contribute to a better understanding of the toxicity of such insecticides to *Am* bees, now become the symbol of biodiversity.

*Speaker

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Poster 45

In silico Identification of Potential TRPM7 Inhibitors for the Treatment of Pancreatic Ductal Adenocarcinoma

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Pancreatic cancer is projected to become the second leading cause of cancer-related mortality by 2030. Approximately 90% of pancreatic cancers are pancreatic ductal adenocarcinomas (PDAC), which affect the exocrine portion of the pancreas. The mortality rate associated with PDAC is very high, primarily because it is often diagnosed at an advanced stage. Surgery is the only treatment that can improve the 5-year survival rate to around 20%, but this option is available to fewer than 15% of patients. Consequently, PDAC represents a significant public health challenge, highlighting the urgent need for a better understanding of its development. Our collaborators' research has identified an overexpression of the cation channel TRPM7 (Transient Receptor Potential Cation Channel Subfamily M Member 7) in PDAC, which correlates with poor patient survival. TRPM7 is a non-selective cation channel that plays a key role in the intestinal absorption of divalent cations and in the maintenance of intracellular magnesium (Mg^2+) homeostasis. The TRPM7 protein also contains a functional kinase domain at its C-terminus, which belongs to the α-kinase family. Our collaborators have shown that TRPM7 contributes to the migration and invasion of pancreatic cancer cells. Currently, no specific inhibitors targeting the kinase activity of TRPM7 are available. The only compound described in the literature, TG100-115, inhibits both the channel and the kinase domains simultaneously, thus lacking selectivity. To identify novel and selective inhibitors of the kinase domain, we performed an *in silico* screening using the CERMN chemical library. This virtual screening led to the selection of approximately ten compounds, which were subsequently evaluated *in vitro*. These assays identified a class of molecules capable of specifically inhibiting the kinase domain of TRPM7.

*Speaker

Poster 46

Regioselective Carboxymethylation of Dextran: Mechanistic Insights for heparan sulfate mimetic (RGTA®) Synthesis

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ReGeneraTing Agents (RGTA®) are synthetic polysaccharides designed to mimic the structural and functional properties of heparan sulfates (HS), an essential component of the extracellular matrix which is degraded during tissue injury. Among them, OTR4120—marketed as the medical device CACIPLIQ20®—is synthesized from a dextran backbone (α(1–6)-linked glucose units) chemically modified by carboxymethylation followed by sulfation. These chemical modifications introduce variations in the substitution patterns across glucose units, leading to a heterogeneous distribution of functional groups along the polymer chain. The initial carboxymethylation step, a bimolecular nucleophilic substitution (SN2) reaction targeting hydroxyl groups on glucosidic units, was identified as the key stage influencing the structure of the precursor influencing the subsequent sulfation, which is crucial for the final product's biological activity. Interestingly, significant regioselectivity was observed during this carboxymethylation, as characterized by 13C HMR spectroscopy (100 MHz) of the carboxymethyl dextran (CMD) precursor. To elucidate its origin, we conducted mechanistic studies using quantum mechanical (QM) simulations. QM simulations have allowed to estimate the activation energies for the carboxymethylation of the different hydroxyl groups within the aqueous solvent, revealing a clear preference for certain reaction pathways. Furthermore, to fully understand the selectivity within the polymeric context, molecular dynamics simulations were performed on various polysaccharide fragments. These allowed us to evaluate the accessibility of the different reactive sites depending on the substitution state of the polymer. Altogether, these results provide new insights into the complex reaction mechanism and open perspectives for the rational design of chemical modifications on dextran and its derivatives.

*Speaker

Poster 47

Retrospective evaluation of molecule enumeration methods

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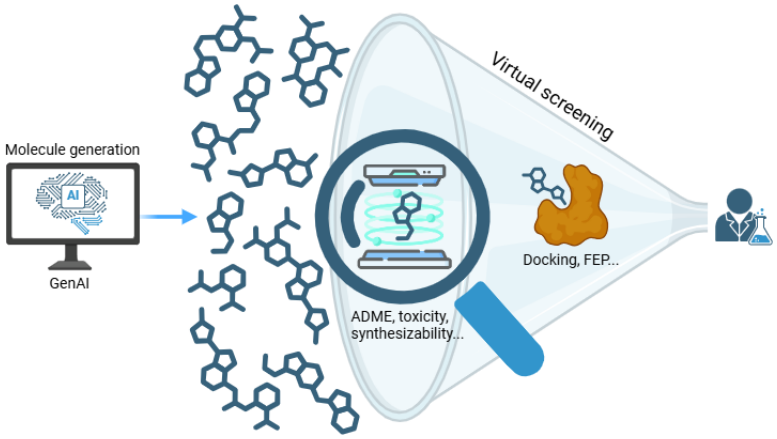
With the advancements of in-silico methods in terms of speed and accuracy, we are able to triage large sets of novel compound ideas. Generating those compound ideas to feed into in-silico triaging methods is a critical step that significantly influences the success of the entire drug discovery process (Figure 1). Therefore, it is crucial to employ enumeration tools that ensure the generation of high-quality molecules while thoroughly exploring chemical space. Various methodologies and tools have been developed for molecular enumeration, ranging from matched molecular pair (1) and reaction-based methods to generative AI (GenAI) (2,3). Evaluating and benchmarking these tools is challenging due to their distinct strengths and weaknesses and limited objective means to evaluate those methods (4,5). Nonetheless, their usefulness can be assessed by analyzing metrics such as the physicochemical properties, drug likeness (6), synthesizability, diversity, and similarity of the enumerated molecules to previously synthesized target compounds, alongside determining the percentage of compounds filtered out by standard in-silico filters. We present a retrospective analysis of a diverse range of enumeration tools on industrial projects. Based on this analysis, we propose guidelines for selecting the most suitable tools to achieve specific objectives, such as evading intellectual property, optimizing molecular properties, performing scaffold hopping, or growing a specific vector. Among other findings, we note that GenAI tools can adapt to diverse applications by leveraging reinforcement learning on ligand-based model predictions (QSAR, MPO) or structure-based, physics-aware approaches.



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Poster 48

Structure-based design of next-generation therapeutics targeting the TSP-1:CD47 complex

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Thrombospondin-1 (TSP-1) is a multifunctional extracellular matrix glycoprotein involved in various physiopathological processes and is considered a key actor within the tumor microenvironment. The interaction between TSP-1 C-terminal domain and its membrane receptor CD47 is crucial for tumor growth (1). Previous studies based on *in vacuo* modeling (2) suggested that the CD47-binding site on TSP-1 could be buried, requiring an opening of TSP-1 to interact with a specific region of CD47. These results led to the design of the TAX2 peptide to antagonize the TSP-1:CD47 interaction (3). Nowadays, a better description of TSP-1 opening mechanism might help develop next-generation antagonists that block its interaction with CD47 receptor. Using classical all-atom molecular dynamics (MD) simulations, we explored the intrinsic dynamics of each protein considered separately, in a realistic environment. While CD47 exhibited various orientations of its extracellular domain, TSP-1 C-terminal domain did not display any opening motion. These data confirmed that such opening requires larger collective motions, which classical MD may not capture. To address this, a bias-exchange metadynamics protocol was applied to TSP-1 in water, utilizing and combining the four lowest-frequency normal modes as collective variables to predict the opening of TSP-1 and the mutual orientation of the protein partners. Such an enhanced sampling method successfully revealed key conformational states of TSP-1, which provide a structural basis for ligand design. These TSP-1 open conformations are used for AI-based *de novo* peptide binder design and *in silico* screening of large libraries of drug-like molecules. The resulting data are analyzed with Coarse-Grained MD simulations to identify scaffolds that can be optimized for the *de novo* design of new candidates capable of blocking the TSP-1:CD47 interaction.

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*Speaker

Poster 49

Statistical Molecular Interaction Fields: A Fast and Informative Tool for Characterizing RNA and Protein Binding Pockets

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Understanding the physical properties of a macromolecule's binding pocket is crucial in structure-based drug design. One way to gain insights in the possible interactions from a binding pocket is by employing Molecular Interaction Fields (MIF). However, this method typically relies on the use of accurate but very specific probes in their calculations.

Our work consists of developing a simplified approach to MIF generation, denominated Statistical Molecular Interaction Fields (SMIF). These employ concise functional forms parametrized either from consolidated knowledge of the interactions or from a statistical analysis over many PDB structures. We have developed SMIF methods for stacking, hydrogen bonds and hydrophobic interactions and observed that, despite the simplicity of the SMIF models, the resulting fields can be very informative and coherent with established pharmacophoric models.

Given that these are simple models and the code has been carefully optimized, the SMIF calculations are fast and can be performed in batch for multiple binding pockets or even whole macromolecules. Furthermore, in contrast to other methods, the SMIF models are not constrained to proteins only; the same calculations can be currently applied to either proteins or RNA molecules. Therefore, this method opens the possibility to further explore other intermolecular systems, such as lipidic membranes and protein/nucleic interfaces, providing insightful visualizations of their possible interactions.

*Speaker

Poster 50

Challenging protein/lipid force fields: binding of the cell penetrating peptide penetratin on lipid membranes of different composition

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Peptide-membrane interactions are crucial for defining the function of membrane active peptides. Among these latter, cell penetrating peptides (CPP) are able to cross biological membrane by direct translocation, without leading to cell death. CPPs are especially promising in the field of drug delivery since they can carry cargos across the membrane. However, many questions remain regarding their interaction with membranes of different lipid compositions. Penetratin is a specific CPP which has been widely studied experimentally in our laboratory as its translocation property depends on lipid composition. Circular dichroism (CD) and differential scanning calorimetry (DSC) experiments showed that this peptide tightly binds to liposomes made of DMPG anionic lipids, but weakly interacts with liposomes made of DMPC zwitterionic lipids. Reproducing experimental results with computer simulations is key to study the translocation mechanism at the molecular level. In this work, we used replica-exchange molecular dynamics (REMD) to challenge the CHARMM36/CHARMM36m lipid/protein force field. We ran simulations in DMPC and DMPG membranes starting from two different conformations: i) penetratin embedded in the membrane as an alpha-helix, ii) unfolded penetratin outside of the membrane. Interestingly, the two starting conditions converged towards the same result: inserted and folded in an alpha-helix in DMPG, unfolded and loosely inserted in DMPC. Our simulations thus validate the ability of CHARMM36 to reproduce experimental results, even if the starting conformation is far from equilibrium. In order to assess the effect of membrane potential, simulations under an electric field are ongoing. Our work paves the way towards using simulations to understand the influence of various parameters on the translocation mechanism (lipid composition, cooperativity, membrane potential, etc.).

*Speaker

Poster 51

An overview on Scientific Software Development

Yaidel Toledo-González * [1]

[1] Code Craft and Beyond

Having access to the software employed in scientific research is equally important than to the input data and results of the study. Some authors have even suggested that publications could be considered as incomplete and ambiguous without it (1). However, practices and regulations on this regard are inconsistent (2).

Works presenting open source software are among the most widely cited publications (e.g., BLAST (3, 4), and Clustal-W (5)). It is surprising, therefore, that so few papers are accompanied by open software (6), given the benefits it may bring. This phenomenon likely arises from a lack of human resources for such specialized tasks, as well as the challenges scientists encounter in maintaining software once project funding concludes (7). Dependencies evolve, programming languages advance, bugs are discovered, and new features are often needed. Consequently, software can deteriorate relatively quickly (8). Initiatives such as the FAIR -Findable, Accessible, Interoperable, and Reusable- Principles for Research Software (FAIR4RS) (9) pretend to establish common methodologies and workflows (10) to enhance software sustainability and usability. However, a critical question remains: How can we ensure that the software being developed, and tentatively preserved for posterity through Open Access initiatives, is well-written, or at least sufficiently robust to be useful for future users? The relevance of this question increases considering that many scientists learn to code through peer collaboration and self-study, rather than from formal education and training; while 75% of researchers with funding from the U.S. National Science Foundation agency indicated they lacked time for such training (12). Additionally, a 2009 survey (11) found that scientists spend $\geq$30% of their time developing software (on average), and $\geq$40% using it -a number that has likely increased since (13). Nowadays, the most viable solution to maintain scientific software after project funding ceases is collaboration. A free software license would allow everyone to access and contribute to it, a practice that has proven to be exceptionally effective in the FLOSS community. However, the challenges remain when the code is intended for a private license, developers lack time or expertise, among others. In such scenarios, collaboration with independent advisors is an effective solution. On this regard, CodeCraft and Beyond is a pioneering initiative in France. Its objective is to bridge the collaboration gap between academia and independent consultancy; and its mission, to put in value the scientific software being developed inside our universities. This project was born from the necessity to have a tailored solution in the area of scientific software development, where not only computer science skills are needed, but also an understanding of the underlying physical and/or chemical phenomenon.

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Poster 52

Block SMILES: an ordered fragment-based molecular representation derived from SMILES

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Generative chemistry (1) has seen rapid development in recent years. However, models based on string representations of molecules still largely rely on SMILES (2), which were not originally developed for this purpose. A promising direction for improving the performance of language models in generative chemistry is to use fragment-based molecular representations. Notable examples include t-SMILES (3), SAFE (4), and fragSMILES(5).The core principle of string fragment-based representations is to group sequences of tokens into fragments with meaningful features such as retrosynthetically combinable blocks or anchor-linker combinations. Block SMILES differs significantly from previous approaches due to its ability to leverage the SMILES uniqueness problem. This problem refers to the fact that multiple distinct SMILES strings can represent the same molecule, as each unique traversal of a molecule's 2D structure yields a different SMILES. By sampling a large number of randomized SMILES, Block SMILES can find optimal SMILES that maximizes coverage of cleavable bonds and minimizes long-range dependencies. Matching these cleavable bonds with a retrosynthetic fragmentation algorithm allows for the generation of blocks that are both concatenable and annotated with retrosynthetic labels.Using a map of retrosynthetic mergers, these blocks can then be combined through simple concatenation to produce retrosynthetically accessible compounds. This makes Block SMILES particularly promising for traditional algorithms such as Genetic Algorithms or Monte Carlo Tree Search. Additionally, it can be used with large language models like MolGPT (6), especially when paired with Byte Pair Encoding.

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Poster 53

Modeling RNA Methyltranserase 16 for Inhibitor Design

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Facing the current challenges in human health requires a detailed understanding of cellular machinery at the molecular level. Among key regulatory mechanisms, N6- methyladenosine (m6A) has emerged as the most abundant internal modification in eukaryotic protein-coding and non-coding RNAs, regulating gene expression by influencing splicing, stability, and degradation. This modification results from the transfer of a methyl group from S-adenosylmethionine (SAM) to the N6 position of adenosine, positioning m6A RNA methyltransferases (MTases) as central players in the orchestration of gene regulation, as well as promising drug targets. To date, many RNA MTases have been identified, each exhibiting distinct mechanisms specificities. Notably, METTL16 reveals an unique binding mechanism, distinct from other m6A writers such as the METTL3/METTL14 complex. In METTL16, RNA plays a pivotal role in modulating the enzyme's conformation and catalytic activity. Despite its emerging importance, the molecular mechanism of METTL16 remains poorly understood. Structural insights are limited, with no complete crystallographic structures available for the enzyme in its various functional states, highlighting the importance of characterizing these complex dynamics while accounting for RNA flexibility. To do so, we first carried out all-atom standard molecular dynamic simulations of METTL16 complex in its different states, using AI-based structural predictions as starting models. Since we aim at investigating the impact of the RNA conformation, advanced simulations have also been performed using REST2 and gEDES approaches to improve the sampling of on METTL16-RNA complex. Then, we characterized structural changes and extensively analyzed the interfaces to assess both global and local structural dynamics and pocket accessibility. Interface clustering will be used to extract representative structures for further investigations by QM/MM calculations and docking.

Keywords: N6-methyladenosine, METTL16, SAM, RNA flexibility, Molecular Dynamics

*Speaker

Poster 54

Deciphering RNA helicase A (RHA) motions to develop selective and efficient inhibitors

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Human RNA helicase A (RHA, also known as DHX9 and belonging to the DEAD/H helicase superfamily) plays an important role in unwinding the double helix of DNA or RNA before the transcription of cellular genes occurs. In human cells, RHA interacts with RNA polymerase II, transcription factors, and coactivators to regulate the transcription and translation of specific genes. Similarly, many viruses have been shown to exploit this cellular function, as RHA interacts with viral RNA and/or proteins, which allows them to multiply. Moreover, RHA has been identified as an important enzyme that promotes the replication of RNA viruses, such as HIV-1, HTLV-1, dengue, Zika, and SARS-CoV-2. The goal of this project is to better characterize the functional dynamics required for RHA's helicase activity in order to develop selective inhibitors that will ultimately act as antiviral drugs. The intriguing mechanism by which RHA unwinds viral RNA must be investigated, as nothing has yet been described except for the structurally related helicase, *Maleless* (MLE), from Drosophila melanogaster. The current study aims to elucidate the functional mechanism of RHA to develop allosteric inhibitors that prevent its function. Through extensive virtual screening, we have identified and experimentally validated selective and efficient small-molecule inhibitors. However, the mechanisms by which they inhibit RHA are still unknown, as no crystal structure of an RHA/inhibitor complex has been solved. A molecular dynamics study using replica exchange to increase conformational sampling was performed to identify relevant binding sites on RHA as potential target binding sites and reveal the major role of RNA binding domain 2 (RBD2). The ultimate goal is to use these helicase inhibitors to block the replication of many RNA viruses and develop broad-spectrum antiviral drugs.

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