Frontiers in Water Biophysics www.waterbiophysics.eu

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BOOK OF ABSTRACTS AND CONFERENCE PROGRAM

XXVI Course of the International School of Statistical Physics
ETTORE MAJORANA FOUNDATION AND CENTRE FOR SCIENTIFIC CULTURE
http://www.ccsem.infn.it/
Directors: Peter Hanggi, Fabio Marchesoni

WELCOME

A warm welcome to all participants and contributors of the seventh Frontiers in Water Biophysics conference. This year is particularly special, as we celebrate the tenth anniversary of our event in Erice, following the inaugural workshops in Trieste (2010) and Perugia (2012).

As in previous editions, this conference has been made possible through the generous intellectual and practical contributions of many individuals. We sincerely thank the staff at the Ettore Majorana Foundation and Centre for Scientific Culture for their ongoing support and guidance, as well as all colleagues who have participated in past conferences. Our heartfelt gratitude also goes to the members of the Scientific and Organizing Committees for their invaluable insights and dedication.

Since its inception, the Frontiers in Water Biophysics series has undergone continuous evolution. This year marks a significant milestone, rooted in the realization that water is more than a background medium in biological systems; it actively participates in the processes of life. Initially, we understood water as a key component of life, food, and medicine, serving as a plasticizer, solvent, and reactant. Over time, foundational studies have revealed water's central and integral role across nearly all facets of life. Our understanding has deepened through a wealth of experimental and theoretical discoveries.

Building on this momentum, this year's conference, FWB2025, will feature a hands-on Machine Learning session supported by the EuMine COST Action CA22143, aiming to propel us into new computational frontiers.

We are excited to explore new perspectives on the complex nature of water. We believe the Frontiers in Water Biophysics series will continue to inspire innovative ideas, foster meaningful collaborations, and generate impactful scientific advancements. Our shared vision drives us forward with enthusiasm and conviction as we contribute to this ambitious and rewarding socio-scientific endeavor.

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Program

	July 2, Wed	July 3, Thu	July 4, Fri	July 5, Sat	July 6, Sun	July 7, Mon
8:30-8:45		OPENING		EuMINe DAY 1	EuMINe DAY 2	
CHAIR		Chair	Chair	Chair	Chair	
8:45-9:55		Koga	Nakabayashi	Chen	Kartunnen: Hands-on with AI Analyses of Properties of Water	FAREWELL BREAKFAST
9:55-10:35		Yang Yao	Di Donato	Rovigatti	Ruiz Perez	
10:35-11:05		COFFEE BREAK	COFFEE BREAK	COFFEE BREAK	COFFEE BREAK	
CHAIR		Chair	Chair	Chair	Chair	
11:05-11:20		Lupi	Napolitano	Stefani	Chauhan	
11:20-11:35		Staniscia	Auricchio	Hedley	Saeidikia	
11:35-11:50		Matyushov	Bertini	De Simone: Harnessing Deep Learning for Antimicrobial Peptide Design	Malaspina	
11:50-12:05		Santamaria	Iaccarino		De Luca	
12:05-12:45	ARRIVAL and REGISTRATION	Vetri	Mergny		Heyden (R)	
12:45-14:45		LUNCH	LUNCH (12:45-14:15)	LUNCH	LUNCH	
CHAIR		Chair	Chair	Chair	Chair	
14:45-15:45		Sassi	Miyoshi (14:15-15:15)	Hands-On Machine Learning Training (16:05)	Hands-On Machine Learning Training (16:05)	DEPARTURE
15:45-16:25		Sterpone	Petraccone (15:15-15:55)			
16:25-17:00		POSTER + COFFEE BREAK	EXCURSION & SOCIAL DINNER	Pastore (16:05-17:15)	POSTER + COFFEE BREAK (16:05-17:05)	
				COFFEE BREAK (17:15-17:40)	Franzese (17:05-17:45)	
CHAIR		Chair			CLOSING (17:45-18:00)	
17:00-17:40		Djavaheri-Mergny		Chair	FREE TIME	
17:40-18:20	WELCOME PARTY	Amato		Jawerth		
18:20-19:00		Di Fonzo		Catalini		
20:00-	DINNER	DINNER		DINNER	SOCIAL DINNER	

July 3rd – THURSDAY

8:30-8:45 **OPENING**
8:45-9:55 TU1 **K. Koga** *"Phobic and philic: hydrophobic interactions and wetting transitions"*
9:55-10:35 IL1 **Y. Yao** *"The state of water under confinement and at subzero temperatures"*
10:35-11:05 **COFFEE BREAK**
11:05- 11:20 OP1 **L. Lupi** *"Perchlorate at the base of the South Polar Layer Deposits make possible the existence of liquid water on Mars"*
11:20-11:35 OP2 **F. Staniscia** *"Curvature-dependent adsorption of surfactants in water nanodroplets and nanobubbles"*
11:35-11:50 OP3 **D. Matyushov** *"Diffusion of proteins in solutions and dynamics of aqueous electrolytes"*
11:50-12:05 OP4 **A. Santamaria** *"Soft, sticky and dynamic. measuring material properties of biomolecular condensates"*
12:05-12:45 IL2 **V. Vetri** *"Revealing Protein Association through Coupled Fluorescence Spectroscopy and Microscopy"*

14:45-15:45 PL1 **P. Sassi** *"Synergistic Solvent Effects on the Structure and Mechanics of Lipid Membranes"*
15:45-16:25 IL3 **F. Sterpone** *"Proteome dynamics at the cell-death temperature: a picture of life adaptation to different thermal niches"*
16:25-17:00 **COFFEE BREAK + POSTER SESSION**
17:00-17:40 IL4 **M. Djavaheri-Mergny** *"Therapeutic Potential of Cationic Amphiphilic G4 Ligands in Cancer Treatment"*
17:40-18:20 IL5 **J. Amato** *"Non-canonical nucleic acid structures: From biophysical characterization to personalized medicine"*
18:20-19:00 IL6 **S. Di Fonzo** *"Exploring the Unfolding Mechanisms of DNA G-Quadruplexes Induced by temperature Using 2D UV Resonant Raman Spectroscopy"*

July 4th – FRIDAY

8:45-9:55 TU2 **T. Nakabayashi** *"Raman bands of water: quantifying water density and biomolecules in a liquid droplet and a living cell"*
9:55-10:35 IL7 **M. Di Donato** *"Self-assembled nanoparticles for photoinduced therapies and energy harvesting"*
10:35-11:05 **COFFEE BREAK**
11:05- 11:20 OP5 **E. Napolitano** *"Tuning the properties of an anti-hmgb1 g-quadruplex-forming aptamer by covalent dimers"*
11:20-11:35 OP6 **D. Auricchio** *"Exploring G-Quadruplex/i-Motif co-localization in B-DNA context"*
11:35-11:50 OP7 **L. Bertini** *"A SAXS-guided extremely coarse grained Montecarlo simulation approach to investigate G4 multimeric structures"*
11:50-12:05 OP8 **N. Iaccarino** *"Design of experiments in solution biophysics: a case study on i-Motif DNA"*
12:05-12:45 IL8 **J.L. Mergny** *"Quadruplexes are everywhere!"*

14:45-15:45 PL2 **D. Miyoshi** *"Structure-dependent hydration and phase separation of nucleic acids"*
15:45-16:25 IL9 **L. Petraccone** *"Biophysical insights into complex folding/unfolding pathways of G-quadruplexes"*
EXCURSION & SOCIAL DINNER

July 5th – SATURDAY – EuMINe DAY 1

8:45-9:55 TU3 **X. Chen** *"Nanoconfined water: unlocking reconfigurable structures beyond biological limits"*
9:55-10:35 IL10 **L. Rovigatti** *"Using entropy to control phase separation in associative polymers"*
10:35-11:05 **COFFEE BREAK**
11:05- 11:20 OP9 **S. Stefani** *"Solvent-driven structural modulation of Diphenylalanine assemblies revealed by micro-FTIR imaging"*
11:20-11:35 OP10 **J. Hedley** *"Electric field of DNA: who is in charge?"*
11:35-12:45 TU4 **A. De Simone** *"Harnessing deep learning for antimicrobial peptide design"*

14:45-16:05 **A. De Simone** ***Hands-on machine learning training***
16:05-17:15 TU5 **A. Pastore** *"The role of water in protein folding"*
17:15-17:40 **COFFEE BREAK**
17:40-18:20 IL11 **L. Jawerth** *"Fiber growth and glass-like aging: two mechanisms through which protein condensates age"*
18:20-19:00 IL12 **S. Catalini** *"Self-assembly behavior of a pure short peptide and its dye-functionalized variants"*

July 6th – SUNDAY – EuMINe DAY 2

8:45-9:55 TU6 **M. Kartunnen** *"Analyzing structural properties of water (and other molecules) with AI/ML"*
9:55-10:35 IL13 **L. Ruiz-Perez** *"Protein dynamics landscapes: liquid phase transmission electron microscopy explores misfolding and aggregation in water"*
10:35-11:05 **COFFEE BREAK**
11:05- 11:20 OP11 **N.P. Chauhan** *"Brownian dynamics of disordered proteins in nanoconfined environments"*
11:20-11:35 OP12 **Z. Saeidikia** *"Hinting at secondary nucleation dynamics in amyloid beta by combining liquid-phase TEM and MD simulations"*
11:35-11:50 OP13 **R. Malaspina** *"pH-induced conformational transition in regenerated silk fibroin and its application to bio-based 3D printing"*
11:35-11:50 OP14 **G. De Luca** *"Probing water ordering in liquid-liquid phase separation phenomena"*
12:05-12:45 IL14 **M. Heyden** *"Anharmonic low-frequency vibrations in the hydrogen bond network of water"*

14:45-16:05 **M. Kartunnen** ***Hands-on machine learning training***
16:05-17:05 **COFFEE BREAK + POSTER SESSION**
17:05-17:45 **G. Franzese "***Machine Learning, experiments, multiscale simulations and theory for hydrated protein-nanoparticle coronas"*
17:45-18:00 **CLOSING**
FREE TIME & SOCIAL DINNER

TUTORIALS

PHOBIC AND PHILIC: HYDROPHOBIC INTERACTIONS AND WETTING TRANSITIONS

Kenichiro Koga

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This lecture reviews the fundamental theories for understanding the physical properties and interfacial phenomena of aqueous solutions driven by hydrophobicity and hydrophilicity. It then discusses recent research on hydrophobic interactions, ion-specific effects, and wetting transitions at interfaces.

The hydrophobic effect encompasses two phenomena: the low solubility of hydrophobic solutes in water and the hydrophobic interaction, a solvent-induced interaction between hydrophobic molecules or moieties critical to biological systems [1,2]. Is it obvious that a hydrophobic attractive interaction arises between solute molecules that repel water [3]? Does the nature and the mechanism of the hydrophobic effect change qualitatively depending on the solute size? We will discuss these important questions. Adding certain electrolytes to an aqueous solution induces aggregation or phase separation of hydrophobic solutes (salting-out), while others promote solubility (salting-in). Such ion-induced changes in physical properties are referred to as ion-specific effects. The fundamental theories for understanding the ion-specific effects are reviewed. Wetting transitions are phase transitions at interfaces [4]. They occur at solid surfaces and at fluid interfaces. From a theoretical perspective, wetting transitions are a transition between two distinct states in a three-phase equilibrium system, governed by the balance of interfacial tensions. Density functional theory provides critical insights into these phenomena. These topics form the foundation of the lecture.

Building on this foundation, recent research on the solute-size dependence of hydrophobic interactions and ion-specific effects in hydrophobic interactions will be introduced [5,6]. Regarding wetting transitions, we will first discuss critical wetting (Cahn's hypothesis), which is a widely accepted phenomenon, and then examine, based on mean-field density functional theory, whether critical wetting is an inevitable phenomenon or not [7].

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RAMAN BANDS OF WATER: QUANTIFYING WATER DENSITY AND BIOMOLECULES IN A LIQUID DROPLET AND A LIVING CELL

Takakazu Nakabayashi

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We have quantified intracellular environments and biological molecules using the Raman bands of water [1-4]. In this talk, we show our recent Raman results on evaluating the water density in a living cell and the chemical properties of liquid-liquid phase separation (LLPS) in solutions and living cells.

[Water density in a cell] We have shown that the water density in a cell can be evaluated using the O-H stretching Raman band of intracellular water [1]. The Raman image of the O-H band shows higher intensity in the nucleus than in the cytoplasm in a living HeLa cell, indicating that the water density in the nucleus is higher than in the cytoplasm. Water density in the nucleus was evaluated to be ~3% larger than that in the cytoplasm. This result indicates that the concentration of biomolecules in the nucleus is lower than that in the cytoplasm. We have proposed that molecular crowding in a cell can be evaluated using the Raman image of water at each organelle.

[LLPS in a buffer solution] LLPS is a water/water phase separation in which highly concentrated liquid droplets of specific biomolecules are generated. LLPS has been used to explain various biological phenomena. We have demonstrated a label-free method to determine the protein concentration in a single liquid droplet using the Raman band of water [3]. We applied our method to LLPS of the low-complexity (LC) domain of FUS, which is one of the ALS-associated proteins (Fig. 1). The Raman bands due to FUS LC were observed only inside the droplets, and only water Raman bands were observed outside the droplets, confirming the condensation of FUS LC in the droplets. The protein concentration inside the single droplet was quantified using the Raman band of outside water as an intensity standard. We quantified changes in the protein concentration with varying solution environments such as pH and salt concentration. We found that FUS LC was highly concentrated to be 13-15 mM in the droplets, and the inside protein concentration decreased as the conditions became less favorable for LLPS.

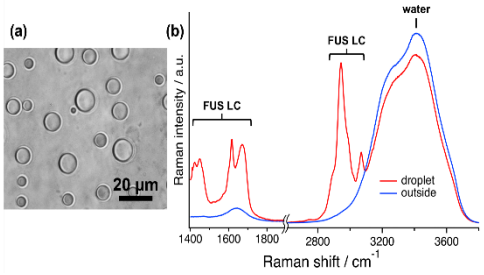

Fig. 1. (a) A bright field image of FUS LC droplets. (b) Raman spectra of inside and outside of the droplet.

[LLPS in a living cell] We applied the quantification method to droplets in living cells [4]. Concentrations of proteins and other components in intracellular droplets were determined. In particular, nucleic acids were found to be highly concentrated in several types of intracellular droplets. These results are difficult to be obtained using other optical methods.

References

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NANOCONFINED WATER: UNLOCKING RECONFIGURABLE STRUCTURES BEYOND BIOLOGICAL LIMITS

Xi Chen

Advanced Science Research Center (ASRC) at the Graduate Center, City University of New York
Department of Chemical Engineering, City College of New York

In nature, plants have developed hydrated materials that mechanically deform in response to changes in relative humidity. These materials, known as 'water-responsive (WR) materials', can harness evaporation and convert it into force or locomotion to drive essential plant tasks, such as the opening of pinecones to release seeds when the environment is dry. Several of these mechanically robust, yet flexible structures can actuate more powerfully than existing actuators and muscles and they hold promise as efficient actuators for energy harvesting, adaptive structures, and soft robotics.

Here, I will discuss our recent studies on deciphering powerful and efficient WR actuation in biological systems and replicating these mechanisms outside the biological context for engineering applications. Inspired by nature, we have developed biomimetic, simplified structures, such as peptide crystal hydrates, that allow fundamental studies across molecular to macroscopic length scales. Using these approaches, we have discovered that, during water-responsiveness, the properties of nanoconfined water/liquids play a dominant role in the energy conversion from the chemical potential of water to mechanical energy. Our fundamental studies have led to the development of high-performance WR materials, as well as the evaporation energy harvesting devices that run autonomously when placed at a suitable air-water vapor interface. This allows for direct energy harvesting from naturally occurring or engineered water evaporation and subsequent conversion into mechanical energy or electricity. Such energy harvesting systems provide pioneering methods to harness the untapped energy source of water evaporation.

HARNESSING DEEP LEARNING FOR ANTIMICROBIAL PEPTIDE DESIGN

Alfonso De Simone

Department of Pharmacy, University of Naples, Italy

The recent exponential growth of deep learning (DL) and other AI technologies has enabled the advance of many research areas, enabling new sophisticated data analysis, fostering innovative approaches to complex scientific questions, and expanding the horizons of research studies across various scientific fields.

DL has significantly contributed to the success of the de novo design of proteins, which was recognized by the 2024 Nobel Prize in Chemistry. One area of impact of DL is the definition of peptide sequences with antimicrobial activity. These are accelerating the discovery and development of novel strategies to face important challenges such as antibiotic resistance or water purification.

The tutorial and hands-on training will be focused on the use of DL to generate antimicrobial peptide sequences with enhanced activity and selectivity to employ in biomaterials for water purification.

THE ROLE OF WATER IN PROTEIN FOLDING

Piero Andrea Temussi[1], Annalisa Pastore[2,3]

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[3]The Wohl Institute, King's College London, 5 Cutcombe Rd, SW59RT London, UK

Water plays a fundamental and intricate role in the life (and death) of proteins, especially during the critical processes of folding into their functional forms and unfolding back into disordered states. Far from being just a passive background medium, water actively shapes the energy landscape that proteins explore as they fold and unfold.
In my presentation, I will discuss the role of water in cold, heat and pressure denaturation using yeast frataxin (Yfh1) as a model system. Yfh1 is a small natural protein that has the unusual property of undergoing cold denaturation at temperatures above the freezing point of water when under conditions of low ionic strength. This peculiarity, together with a remarkable resilience, allows the determination, for the whole protein as well as for individual residues, of the stability curve, that is the temperature dependence of the free energy difference between the unfolded and folded forms. The ease of measuring stability curves without the need of adding denaturants or introducing ad hoc destabilizing mutations makes this protein an ideal "tool" for investigating the influence of many environmental factors on protein stability. In my talk, I will recapitulate some of the open questions that Yfh1 has helped to address, including understanding the differences and commonalities of the cold, heat and pressure unfolded states. This protein thus offers a unique tool for studying aspects of protein stability so far considered difficult to assess and provides important guidelines that could allow the identification of other similar systems.

ANALYZING STRUCTURAL PROPERTIES OF WATER (AND OTHER MOLECULES) WITH AI/ML

Mikko Karttunen

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Despite its abundance on earth, water is one of the most curious substances and it keeps on providing surprises [1-3]. From the computational perspective the number of different water models is nothing short of mind-blowing, but despite constant improvements, the development continues. In this lecture, we will focus on some potential new analysis methods for the structure and dynamics of water. In particular, we recently introduced a machine learning (ML) workflow and method to characterize structural properties of molecules and systems [4]. While the original work was in the context of lipids, and phase transitions in lipid systems, the method is general and not limited to any particular system. As an example, we recently used the same approach to connect scanning tunneling microscopy data with ML-driven simulations [5]. In this lecture, we discuss the detailed background of the method in the context of some other methods, and in the computer lab session we will apply the method to analyze water. I will also provide a very brief review on some of the curious properties of water.

M.K. thanks the Natural Sciences and Engineering Research Council of Canada (NSERC) and the Canada Research Chairs Program. Digital Research Alliance of Canada provided the computing facilities

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PLENARY LECTURES

SYNERGISTIC SOLVENT EFFECTS ON THE STRUCTURE AND MECHANICS OF LIPID MEMBRANES

Paola Sassi

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Biomembranes are highly functional sites within living systems and are crucial to many fundamental processes, including material transport, recognition, adhesion, and signaling. They exhibit unique surface and mechanical properties due to their interaction with water. Any additive able to change lipid-solvent interactions can impact on the structure and function of the lipid bilayer. Therefore, understanding membrane solvation is essential for studying both model and biological systems [1].

Dimethyl sulfoxide (DMSO) is a universal water-soluble solvent widely utilized in various biotechnological and medical applications, such as cell cryopreservation and the treatment of different human diseases (e.g., amyloidosis) [2]. As a cryo-preservative agent, its effects are primarily associated with its action on the plasma membrane, particularly under low-temperature conditions [3]. Despite the numerous studies reported, the effects of DMSO on the physicochemical properties of biological membranes remain poorly understood.

We investigated how this co-solvent influences the structural and thermotropic properties of model membranes across varying compositions. In different lipid systems, where the transition from the gel to the liquid disordered phase of the membrane can be identified, we monitored the thermal stability of the gel phase and its relationship to the dehydration of both the polar and interfacial regions of the bilayer (lyotropic effect) using an ensemble of techniques, namely Infrared spectroscopy, Differential Scanning Calorimetry, and fluorescence spectroscopy [4,5]. We found that DMSO decreases the cooperativity of the main phase transition by broadening the melting range and reducing the thickness of the lipid bilayer. Membrane thinning reduces the solubility (and potentially the mobility) of small apolar molecules within the bilayer and modifies the flexibility of the membrane. We performed Flicker spectroscopy to evaluate the mechanical properties of Giant Unilamellar Vesicles, analyzing the effects of both high cholesterol concentration and DMSO. Through Flicker spectroscopy analysis, we obtained bending modulus values for the various samples that correlate with the membrane's remodeling capability, which is essential for cell life and interaction with the external environment. We identified several general aspects regarding the effect of DMSO, which varies with its concentration [6].

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STRUCTURE-DEPENDENT HYDRATION AND PHASE SEPARATION OF NUCLEIC ACIDS

Daisuke Miyoshi

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Liquid-liquid phase separation (LLPS) of nucleic acids has been attracting attention as a novel phenomenon in living cells. Importantly, LLPS should be fundamental for spaciotemporal chemical processes in crowded cellular environments. It is now evident that LLPS involving nucleic acids participates in the regulation of the central dogma at various levels, such as replication, transcription, processing, and translation. Dysfunction of LLPS is linked to the onset of neurodegenerative diseases as well as viral infection and cancer.

We have biophysically studied properties of nucleic acids under cell-mimicking conditions [1]. It was demonstrated that molecular crowding destabilizes and stabilizes the canonical (duplex) structure and the non-canonical structures, respectively, of nucleic acid structures [2]. Especially, G-quadruplex is significantly stabilized by molecular crowding, indicating its importance in regulation of gene expression. These results indicate that nucleic acids show structural polymorphism, depending on cellular environmental factors, thus nucleic acids structures further can play a regulatory role in LLPS. In this study, we will deliver hydration state of nucleic acids under cell-mimicking molecular crowding conditions. Then, we will introduce a LLPS model system using G-quadruplex-forming oligonucleotides and cationic peptides [3]. Finally, we would like to discuss how to control LLPS of nucleic acids by using oligonucleotide, peptide, epigenetic modification, and small molecules targeting the nucleic acid structures [4].

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INVITED LECTURES

THE STATE OF WATER UNDER CONFINEMENT AND AT SUBZERO TEMPERATURES

Yang Yao

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Water is the most ubiquitous and essential liquid on earth, and it is fundamental to the existence of life. Many biological processes take place in crowded aqueous surroundings and water in living cells can be considered as confined water. However, water behaves differently under confinement with respect to the crystallization and dynamics compared to those in the bulk. Especially in biological systems, the role of confined water is of crucial importance though still far from fully understood. In this talk, I will first present the understanding of water in hard confining media provided by hollow silica spheres and mesoporous silica. Then, I will present our recent finding on water under soft confining media provided by lipidic mesophase (LMP). A commercially available lipid, phytantiol, was recently discovered that gives the access to the liquid water in LMPs at subzero temperatures. The comprehensive understanding on the crystallization and dynamics of water confined in the lamellar phase were obtained from differential scanning calorimetry and broadband dielectric spectroscopy. Two dynamically different fractions of water were observed that are assigned to a slower bound water close to the head group of the lipid and a faster interstitial water inner the lamellar channel. In the talk, I will also present the evidence for the potential application of the cryogenic liquid water in LMPs on cryo-enzymatic reactions. In the end, I will discuss the recent understanding on the state of water and the dynamics of lipids during the phase transition in LMPs from the cubic to the reverse hexagonal phase.

References

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REVEALING PROTEIN ASSOCIATION THROUGH COUPLED FLUORESCENCE SPECTROSCOPY AND MICROSCOPY

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Protein association assembly is a complex phenomenon which leads to the formation of functional structures with unique properties. The concept of emulating these processes to design nature-inspired biomaterials, for applications like drug delivery or sensors, is now gaining attention.
The deep comprehension of the molecular mechanisms and fundamental laws underlying protein condensation and aggregation is essential to grasp the rules regulating their biological function/disfunction and to rationalize the design of biomimetic materials.
The fruitful combination of fluorescence spectroscopy and microscopy constitutes a powerful method for monitoring protein liquid-liquid phase separation and aggregation processes. This approach provides molecular insights that are often elusive with bulk methods. The lecture will focus on how the phasor approach can be used to analyze spectra and FLIM-based lifetime measurements of environment-sensitive probes to obtain pixel-resolution maps of the molecular structures of protein assemblies and the surrounding water network.

PROTEOME DYNAMICS AT THE CELL-DEATH TEMPERATURE: A PICTURE OF LIFE ADAPTATION TO DIFFERENT THERMAL NICHES

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Temperature is a boost for cellular metabolism but above a threshold it corrupts functional processes involving proteins and causing cell death. Whether the thermal denaturation involves the whole proteome or just a subset of critical proteins in the cytoplasm is still debated. Here, we attack the problem from a preferential angle by monitoring via QENS and multi-scale simulations the dynamical state of the E.coli proteome across the cell death temperature. Above the cell death the cytoplasm experiences a dynamical slowdown caused by the unfolding of just a small number of proteins. This small fraction is sufficient to induce a gelation of the cytoplasm. From the dynamical properties the fraction of unfolding is extracted and used to reconstruct successfully the E. coli growth rate. Based on this finding, the analysis is extended to extremophilic bacteria, adapted to cold and hot environments. The dynamical properties of the proteomes, sampled at different timescales, point to the fact that temperature adaptation is strongly connected to cytoplasm viscosity, and that the depending on the organism, thermal corruption of metabolism is differently connected to the proteome stability.

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THERAPEUTIC POTENTIAL OF CATIONIC AMPHIPHILIC GUANINE QUADRUPLEX LIGANDS IN CANCER TREATMENT

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Cationic amphiphilic drugs (CADs) are small molecules characterized by one or more hydrophobic groups along with a polar domain that includes a basic amine. CADs passively diffuse through cellular membranes into the acidic lysosomal compartments, where they become protonated due to the low pH environment. This process prevents the diffusion of CADs back into the cytosol leading to their accumulation within lysosomes, a phenomenon termed lysosomotropism. Once inside lysosomes, high doses of CADs alter lysosomal pH and disrupt lipid metabolism, leading ultimately to lysosomal membrane permeabilization and cell death [1].

Several anticancer compounds such as mitoxantrone, doxorubicin and daunorubicin exhibit lysosomotropism, a process that prevents them from reaching their primary targets, thereby contributing to resistance of cancer cells to therapy [2].

We recently reported the unexpected ability of some Guanine-quadruplex (G4) ligands that target DNA to accumulate in lysosomes leading to lysosomal membrane permeabilization (LMP) and the subsequent activation of cellular stress adaptation pathways. Notably, the combined treatment between a G4 ligand and chloroquine (a lysosomal function inhibitor) resulted in pronounced lysosomal membrane permeabilization coupled to massive cell death [3,4]. Altogether, our results reveal an unanticipated lysosome-related mechanism that contributes to cancer cell resistance to G4 ligand and propose a strategy to overcome this resistance.

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NON-CANONICAL NUCLEIC ACID STRUCTURES: FROM BIOPHYSICAL CHARACTERIZATION TO PERSONALIZED MEDICINE

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In the ever-evolving landscape of biomedical research, G-quadruplex (G4) nucleic acid structures have emerged as fascinating therapeutic targets for precision medicine and molecular diagnostics. These noncanonical arrangements of DNA or RNA play crucial roles in gene expression regulation and are implicated in the pathogenesis of various diseases, including cancer [1]. Integrative analyses of mutations found in patient-derived tumor cells, combined with assessments of differentially G4-enriched genomic regions, have linked G4s to cell-type specific transcriptional control, tumor heterogeneity, and genome instability [2]. G4-interacting ligands show potential for therapeutic modulation of G4 biology. However, precise targeting of specific G4 structures is essential for clinical translation. Developing ligands with enhanced affinity and specificity is essential to realize the full therapeutic potential of G4-targeting strategies [3,4]. To fully understand and exploit G4 interactions, it is crucial to study them in physiologically relevant conditions, where water plays a fundamental role. The latest advances in this research field will be discussed, along with strategies for enhancing the specificity and effectiveness of G4-targeting ligands, considering the crucial influence of the physiological environment on G4 stability and interactions.

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EXPLORING THE UNFOLDING MECHANISMS OF DNA G-QUADRUPLEXES INDUCED BY TEMPERATURE USING 2D UV RESONANT RAMAN SPECTROSCOPY

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IUVS beamline, Elettra - Sincrotrone Trieste S.C.p.A. S.S. 14 km 163,5 in AREA Science Park, Basovizza, Trieste, Italy

G-quadruplexes are polymorphic nucleic acid structures with key biological functions. This study examines the thermal unfolding of four biologically relevant G-quadruplex DNA sequences using UV resonance Raman (UVRR) spectroscopy and advanced spectral analysis. Single-value decomposition identified distinct states, while 2D correlation techniques (PCMW2D and 2D-COS) revealed sequential unfolding events. The findings highlight unique hydrogen-bond disruptions and conformational transitions, demonstrating UVRR spectroscopy's capability to resolve molecular structural changes and enhance understanding of G-quadruplex stability.

IL7

SELF-ASSEMBLED NANOPARTICLES FOR PHOTOINDUCED THERAPIES AND ENERG HARVESTING

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Self-assembled nanoparticles of organic chromophores often present peculiar properties, which can make them suitable candidates for different applications, going from nanomedicine to optoelectronic and solar light harvesting.
Water induced aggregation in most cases results in notable changes of the spectroscopic properties of organic dyes, such as super-radiance, spectral shifts or exceptional energy transport capability.
In the biomedical field, self-assembled nanoparticles have been recently used in applications related to photodynamic or photothermal therapies for cancer treatment, because of their ability to generate reactive oxygen species or localized temperature increases determining cellular death. I will present several examples of systems that we recently analyzed by performing extensive spectroscopic analysis, both with steady state and time resolved techniques, to understand the molecular mechanisms of their photoinduced behavior.
Moving then to materials which can be interesting for optoelectronic applications, I will then discuss the peculiar excitonic properties of light harvesting nanotubes, formed by the self-assembly of amphiphilic cyanine dyes in water, whose energy transport behavior has been analyzed through a combined ultrafast spectroscopic and theoretical approach.

QUADRUPLEXES ARE EVERYWHERE!

Jean-Louis Mergny

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Water has been known to play a role in nucleic acids structure since the 50's and fiber diffraction data. In this lecture, I will introduce unusual nucleic acid structures such as G-quadruplexes (G4s) which can find applications in biology, medicine, as well as biotech- and nanotechnologies [1]. We are developing tools to understand their folding and polymorphism, both in vitro and in cells [2], as well as the influence of external parameters such as pH, ligands, ionic conditions or hydration. We are seeking new original folds, such as a DNA quadruplex structure with a unique cation dependency [3]. Of special interest for this summer school will be a novel alternative G4 structure we discovered which needs dehydration to form [4]. We will present algorithms for the prediction of these unusual motifs [5] which are now applied to a variety of genomes, including cancer or viral genomes [6].

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BIOPHYSICAL INSIGHTS INTO COMPLEX FOLDING/UNFOLDING PATHWAYS OF G-QUADRUPLEXES

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DNA and RNA G-rich sequences can form noncanonical G-quadruplex (G4) structures, formed by stacking of G-tetrad layers of four guanines locked by Hoogsteen-type hydrogen bonds and further stabilized by monovalent cations such as K^+ or Na^+ [1]. The formation of such structures is involved in the regulation of gene expression as well as in many other cellular processes, including RNA metabolism, epigenetic states, and related diseases [2,3]. Moreover, the biological role of G4s is not limited to humans but extends to yeasts, bacteria, and viruses [4]. Therefore, G4s emerged as promising therapeutic targets for drug development. However, G-quadruplex folding/unfolding pathways can be very complex involving more coexisting conformation at physiological temperature. The study of the thermodynamic factors that determine the relative stability of different conformations is essential to understand the role played by conformational switching in regulate biological processes and/or to design drugs that alter these equilibria by targeting selectively one conformation. Here, as a case study, I will show the comprehensive characterization of the stability and unfolding mechanism of an RNA G-quadruplex formed by the RG1 sequence within the SARS-CoV-2 genome, using a wide range of spectroscopic, calorimetric, and computational techniques. The obtained results indicate that RG1 quadruplex undergoes a complex unfolding process involving an intermediate. A detailed analysis of the unfolding mechanism revealed that, at physiological temperature, the most populated species is the intermediate, rather than the RG1 G-quadruplex conformation. The data are consistent with the intermediate species being a two G-triads RNA triplex, which could serve as a complementary therapeutic target for COVID-19 [5]. Furthermore, the observed ability of RG1 to adopt two alternative non-canonical nucleic acid structures could be the basis of a more complex regulatory switch.

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USING ENTROPY TO CONTROL PHASE SEPARATION IN ASSOCIATIVE POLYMERS

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In the classical picture a gas-liquid-like phase separation occurs between a low-density ("gas") phase that has high entropy and energy, and a high-density ("liquid") phase that has low entropy and low energy. By contrast, in soft matter system the tunability of the building blocks can be exploited to engineer more complex scenarios.
Here I will show how a judicious design of the patterns of reactive monomers along a polymer chain can drive a fully-entropic phase separation in associative polymer systems. I will use numerical simulations to demonstrate that the effect is robust, and rests on the balance between the distinct entropic contributions controlling the binding. I will also provide a theoretical justification and a possible experimental realization of the phenomenon by means of DNA nanotechnology, paving the way for the design of new self-assembling systems, as well as for a better understanding of phase separation phenomena in associative (bio-)macromolecular systems.

FIBER GROWTH AND GLASS-LIKE AGING: TWO MECHANISMS THROUGH WHICH PROTEIN CONDENSATES AGE

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In the past decade, there has been an explosion in biology where it is increasingly recognized that there are biological proteins that phase separate out of solution to form protein-dense droplets, termed 'condensates'. These are found in numerous important biological processes. Increasingly, we find that the exact material nature of the liquid-like condensates (such as their visco-elasticity) is important for proper function in vivo. Interestingly, protein condensates exhibit a range of material properties and behaviors not exhibited by synthetic materials. These include growth into ordered fibers, ultra-low surface tensions, and aging similar to glasses. This diversity of properties and their exact manifestation are ultimately dictated by the amino acid sequence of the proteins that comprise them. Although approaches developed to describe synthetic materials work well to "first approximation", they cannot describe the intricacies and diversity of material behaviors we observe. Developing such an understanding is a very exciting direction for soft condensed matter physics but is also important for our understanding of how biological systems can harness similar principles to achieve specificity. In this talk, I will present two recent experimental studies in which we uncover how condensate material properties evolve over time. In the first, we discovered that many condensates undergo a transition from liquid-like behavior to more solid-like behavior. This transition has some similarities to aging in glasses while also possessing some unique features. In the second study, I discuss our observations of how condensates associated with neurodegeneration transition to form ordered amyloid-fibers over time. Our experimental observations demonstrate that contrary to the currently expected paradigm, condensates may hinder, not promote fibril formation.

SELF-ASSEMBLY BEHAVIOR OF A PURE SHORT PEPTIDE AND ITS DYE-FUNCTIONALIZED VARIANTS

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This study explores how solvent environments influence the self-assembly and structural morphology of Boc-protected diphenylalanine (Boc-FF) and its dye-conjugated variants, with an emphasis on applications in material science. We found that Boc-FF aggregates shape into different morphology (e.g., spheres, plates) based on the balance of water and acetonitrile [1]. Pure organic solvents produce single orthorhombic crystalline phases, while mixtures with water yield both orthorhombic and hexagonal phases [1]. Aromatic stacking and hydrophobic interactions drive the formation of these structures, with specific solvent conditions playing a key role in aggregate morphology. When boron-dipyrromethane (BODIPY) dyes are attached to Boc-FF, the resulting chromopeptides display different optical properties and self-assembly behaviors. Unlike pure Boc-FF, the chromopeptide aggregates morphology is less sensitive to solvent composition. However, they exhibit modified absorption/emission spectra, induced chirality, and accelerated excited-state relaxation, which could make them suitable for photothermal therapy applications [2]. Overall, the study underscores the importance of solvent selection and building block design in developing advanced biomaterials with customizable properties [3].

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PROTEIN DYNAMICS LANDSCAPES: LIQUID PHASE TRANSMISSION ELECTRON MICROSCOPY EXPLORES MISFOLDING AND AGGREGATION IN WATER

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Liquid-phase transmission electron microscopy (LPTEM) offers exceptional capabilities for visualizing time-resolved structures within their native liquid environments, thereby avoiding artefacts commonly associated with conventional drying or cryogenic methods. A fascinating application of LPTEM is the investigation of molecular structures within cells, including proteins. The liquid environment of the sample facilitates the exploration of previously inaccessible protein states, as it allows for the unobstructed movement of delicate structures during imaging. This unique feature enables in situ examination of protein conformational changes, which contributes to advancing research in structural biology.

We employ LPTEM to gain insight into protein aggregation's structural evolution and dynamics, particularly focusing on misfolded proteins such as tau and amyloid beta peptide (Aβ), which readily assemble into amyloid fibrils. This aggregation process is closely linked to Alzheimer's disease (AD) and has been extensively studied; however, direct observation of the microscopic intermediate steps remains highly challenging. By integrating LPTEM with all-atom molecular dynamics simulations, we provide a more comprehensive understanding of protein behavior in solution.

In addition to visualizing protein structure in a hydrated state, we can also extract some information from the dynamic evolution of these structures. We show that tracking changes in Aβ oligomer contours over time enables the characterization of morphological fluctuations. This approach allows us to investigate the mechanical properties of the aggregates, offering insights into their stability. Our findings present the first direct visualization of Aβ oligomer dynamics, protofibril formation, and oligomer-fibril interactions, demonstrating how LPTEM serves as a powerful tool for imaging and identifying key molecular events in Aβ aggregation. This work contributes to a deeper understanding of protein self-assembly, with implications for neurodegenerative disease research and therapeutic development.

ANHARMONIC LOW-FREQUENCY VIBRATIONS IN THE HYDROGEN BOND NETWORK OF WATER

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The dynamics of biomolecules are governed by degrees of freedom capable to exchange energy through thermal collisions. Besides rigid body translation and rotation of molecules, these are highly anharmonic low-frequency vibrations that can result in conformational change. The latter includes collective motions of secondary and higher order structure units of proteins against each other as well as rotations of key dihedral angles. The frequencies associated with such motions range from the diffusive regime (zero frequency) into the far-infrared (10's of cm^{-1}).

This is in stark contrast to high-frequency vibrations in the mid-infrared, whose quantized energy levels are separated by energies substantially greater than k_BT. Interestingly, the H-bond stretch vibration in the hydrogen bond network of water is located right in the transition region between the low- and high-frequency regimes at approximately 200 cm^{-1}, where $hc\tilde{\nu}\approx k_BT$.

A theoretical and computational characterization of anharmonic low-frequency vibrations is challenging due to the absence of convenient analytical models. The theoretical framework of the harmonic oscillator (including derivations) is commonly applied to analyze molecular vibrations. However, the lower the frequency the less valid are the underlying assumptions and biomolecular functions is often tied to the lowest frequency vibrations.

To solve this problem, we recently developed a theoretical framework for the analysis of anharmonic vibrations in molecular simulations, which is free of approximations and enables us to identify all vibrations contributing to the vibrational spectrum at a given frequency (including zero frequency). Our approach, FREquency-SElective ANharmonic (FRESEAN) mode analysis is straightforward to apply to simulations trajectories of large biomolecules, either in atomistic detail or coarse-grained representations. We further extended this approach to enable the analysis of low-frequency vibrations in the hydrogen bond network of water and the hydration shell of proteins. Further, our analysis reveals a distinct role of low-frequency vibrations for the thermal coupling of proteins to their surrounding solvent.

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MACHINE LEARNING, EXPERIMENTS, MULTISCALE SIMULATIONS AND THEORY FOR HYDRATED PROTEIN-NANOPARTICLE CORONAS

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Nanoparticles are opening new perspectives in drug delivery. However, understanding their interplay with biological systems to design new therapeutic strategies is challenging. Through multiscale simulations, we investigate the kinetics of the protein-nanoparticle hard and soft corona [1, 2], which govern the nanoparticle-receptor interaction for drug delivery effectiveness. Starting from lipid nanoparticles, we reveal the critical role of bound and unbound water [3] in their structure [4]. By accounting for the contribution of water, we discuss how nanoparticle chemistry influences protein structural stability and aggregation [5, 6]. By combining machine learning and experiments, we confirm our simulation predictions and provide a new tool to analyze experimental data for the protein corona [7]. We explore how the size of the nanoparticle influences the composition of the protein corona and the slowing down of its kinetics. By mapping the adsorption model onto a Trap Model, we illustrate the conditions under which protein corona kinetics become glassy, with consequences for therapeutic outcomes and the design of effective drug delivery nanodevices [8].

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ORAL PRESENTATIONS

PERCHLORATE AT THE BASE OF THE SOUTH POLAR LAYER DEPOSITS MAKE POSSIBLE THE EXISTENCE OF LIQUID WATER ON MARS

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Ice Ih is the stable form of water under present-day conditions of temperature, atmospheric pressure, and relative humidity on Mars. Nevertheless, using radar sounder MARSIS data, Orosei et al. (2018) detected a bright reflector at the base of the South Polar Layered Deposits (SPLD), which they interpreted to be caused by ponded water or saturated sediments. Lauro et al. (2021) expanded the research confirming the earlier result and detecting three new bodies of water. To explain the presence of liquid water at the base of the SPLD, Orosei et al. (2018) and Lauro et al. (2021) suggested that the water is a saline solution. Salts are abundant in the Martian soil: perchlorates, chlorates (Hecht et al., 2009; Hanley et al., 2012; Glavin et al., 2013) and hydrated chlorides (Ojha et al., 2015) are globally distributed. The main argument against the possible presence of basal briny water is the low temperature inferred at the base of the SPLD (~180K), which was thought to require a large amount of salt to maintain the water in a liquid state (Sori and Bramson, 2019). This requirement has been discarded by new laboratory measurements (Mattei et al., 2022; Stillman et al., 2021). Recent experiments (Stillman et al., 2021) suggest that perchlorate solutions, with moderate salt concentration (>300mM), can generate bright reflections as those detected by MARSIS. Thus, briny water remains the most plausible explanation for the high reflectivity at the base of the SPLD. Here we address the processes responsible for the formation and persistence of substantive bodies of liquid water in the frozen south polar region of Mars by a combination of experimental and computational techniques. To test whether subglacial brines can be in direct contact with the SPLD we carried out extensive molecular dynamics simulation studies of coexistence of ice with salty (perchlorate) water with the direct coexistence technique as a function of temperature and concentration to assess the range of thermodynamic conditions where this coexistence is possible. We determined the equilibrium melting temperature of the salty water and found it to be consistent with experimental data. We investigated the ion rejection mechanism and observed that the ice formed from perchlorate water solution is almost completely salt free. We proved the coexistence between ice and briny water at several temperatures higher than the eutectic, with pure ice growing at the expenses of an increasingly concentrated solution. We also performed extensive dielectric measurements showing that at temperatures close to the eutectic the apparent permittivity of the system is comparable with that of MARSIS. The comparison between experimental and computational results brought us to interpret the bright reflections detected by MARSIS in terms of a coexistence between almost ion-free ice and a highly concentrated briny water that at temperatures as low as the one at the SPLD of MARS are very likely stable or only slightly metastable with respect to the salt crystal.

OP2

CURVATURE-DEPENDENT ADSORPTION OF SURFACTANTS IN WATER NANODROPLETS AND NANOBUBBLES

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Surfactants, molecules that readily adsorb to liquid interfaces and reduce surface tension, have been a focus of scientific research for nearly a century. Nevertheless, while their behavior on flat surfaces is well-studied, their interactions with tiny, curved surfaces, such as those in nano-sized droplets and bubbles, have remained elusive and largely unexplored, primarily due to challenges in direct experimental observation. To shed light on this aspect, we perform molecular dynamics simulations of short-chain surfactants in nanodroplets and nanobubbles (see figure) and investigate how curvature impacts the adsorption at the water-vapor interfaces.

The outcomes reveal that adsorption systematically depends on curvature, being enhanced on droplets and reduced on bubbles, with the effect becoming more pronounced for surfactants with longer hydrophobic tails. We attribute this curvature-dependent behavior to two key mechanisms: Laplace pressure and curvature-dependent surface tension. The breakdown of these contributions allows us to develop a simple theoretical model that offers a quantitative view of these mechanisms and is able to predict the influence of curvature on adsorption, particularly for longer-chain surfactants.

We investigate this phenomenon also in droplets deposited on a substrate, where the effect of curvature remains relevant, but surfactants can be adsorbed also at the water-substrate or at the vapor-substrate interfaces. This has an effect on their shape [1], displaying a strong size-dependent behavior [2].

These results have broad implications across various fields, from cloud formation and climate modeling to the stability and reactivity of nanodroplets and nanobubbles.

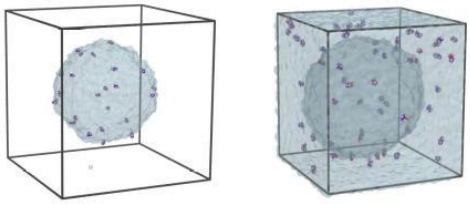

Figure 1. *Simulation snapshots of a droplet (left) and a bubble (right). Surfactants (in this case propanol) are shown in all-atom representation while water is represented as a transparent smoothed density isosurface.*

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DIFFUSION OF PROTEINS IN SOLUTIONS AND DYNAMICS OF AQUEOUS ELECTROLYTES

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Diffusivity of a Brownian particle is caused by random molecular collisions in the Stokes-Einstein picture, but the question of physical forces driving diffusion and mobility of large particles is not addressed. We adopt the Born-Kirkwood view to study physical forces that drive protein diffusion as a result of random imbalances between electrostatic and van der Waals (vdW) forces. They turn out to be remarkably strongly correlated, both statistically and dynamically. There is a nearly exact compensation relation between the variance of the electrostatic force and the cross vdW/electrostatic correlation. The dynamic cross-correlation is even more dramatic: vdW and electrostatic forces relax on the same time scale of a few nanoseconds separated by six orders of magnitude from the relaxation time of the total force. Compensation relations make diffusion constant nearly insensitive to protein charge as demonstrated for charge mutants of green fluorescent proteins (GFPs) with the charge changing from -29 to +35 [1]. When one further considers mobility of micrometer-scale particles, interfacial dielectric constant and asymmetry of the interfacial water response, a nonlinear dielectric effect, determines electrophoretic mobility [3]. These ideas equally apply to concentrated electrolytes of simple ions. The diffusion constant decreases with the electrolyte concentration, but the effect is purely dynamic and caused by the altering memory time of electrolyte ions [3].

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OP4

SOFT, STICKY AND DYNAMIC. MEASURING MATERIAL PROPERTIES OF BIOMOLECULAR CONDENSATES

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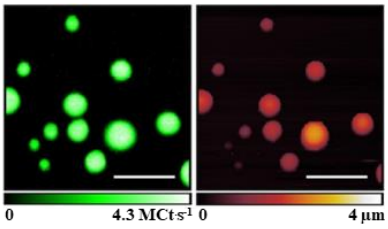
Biomolecular condensates have recently emerged as a new paradigm of subcellular compartmentalization. Viscosity and surface tension govern their structure and dynamics and are pivotal in describing condensates' biological functions. Surface tension is usually estimated with optical tweezers, limited to the piconewton-range. Passive microrheology, which relies on tracking fluorescent beads embedded within condensates, can assess viscosity, but it is influenced by condensate internal inhomogeneities and the bead size. Following coalescence events provides the ratio viscosity/surface tension but requires micrometric and optically visible droplets. Finally, Fluorescence Recovery After Photobleaching (FRAP) can estimate the diffusion coefficient of the condensed-phase component. Combined with confocal and Atomic Force Microscopy (AFM), as illustrated in the Figure, we used it to probe molecular diffusion within condensates formed by the plant protein ELF3 and differentiate between liquid- and gel-phase droplets, characterized by a distinct mechanical response. However, interpreting FRAP curves is non-trivial in the case of multicomponent condensates.

To overcome the limitations of conventional approaches, we developed a method named FRAP-ID (Fluorescence Recovery After Probe-Induced Dewetting), which provides accurate values of condensate mechanical properties. We determined surface tension by measuring the attractive force that a condensate confined between the support and the tip of an AFM cantilever exerts on the latter. The resulting values ranged from 10^{-5} to 10^{-3} $N \cdot m^{-1}$, depending on the specific phase-separating protein. Additionally, we used the AFM tip to dewet regions within fluorescent condensates, and epifluorescence microscopy to monitor the rewetting time. The latter, governed by fluid mechanics, as described by Tanner's law, accurately leads to the ratio surface tension/viscosity. Therefore, previous estimation of the surface tension allows us to determine viscosity in the range of tens $Pa \cdot s$. Lately, we have been working on a novel methodology to evaluate condensate density by determining their volume through epifluorescence microscopy and employing AFM cantilevers as picobalances to estimate their mass (picogram-range). This approach enables tracking condensate mass variations over time with a resolution of few molecules per ms, evaluating the molecular transfer between phases.



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OP5

TUNING THE PROPERTIES OF AN ANTI-HMGB1 G-QUADRUPLEX-FORMING APTAMER BY COVALENT DIMERS

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High-Mobility Group Box 1 (HMGB1) is a ubiquitous nuclear protein present in almost all eukaryotic cells [1,2]. In inflammatory conditions, HMGB1 is secreted from immune cells in the extracellular environment acting like a cytokine [3]. Once released, it can mediate various cellular responses, including cell migration/proliferation and release of other pro-inflammatory cytokines [4]. Moreover, HMGB1 contributes to various chronic inflammatory and autoimmune diseases as well as of cancer [5]. Given the crucial roles of HMGB1 in these pathologies, identification of inhibitors of this protein is of huge clinical interest [6]. In this frame, we recently identified a set of 14 G-quadruplex (G4) forming aptamers as potential HMGB1 inhibitors, using SELEX [7] from a properly designed G-rich oligonucleotide library. Then, we fully characterized the aptamers and evaluated their interaction with HMGB1, together with their ability to inhibit HMGB1-induced migration in cancer cells. The obtained results led us to conclude that the best-performing aptamers were the ones able to spontaneously form dimeric parallel G-quadruplex structures and the most bioactive one was the aptamer named L12 [8,9].
Here, we report the design, synthesis and characterization of a set of covalently-linked L12 dimers, containing connecting linkers of different chemical nature and length, aiming at identifying derivatives of this aptamer with improved properties in view of both therapeutic and diagnostic applications in HMGB1-related pathologies. Several biophysical techniques were used to investigate their conformational behavior, molecularity and stability. Moreover, the interaction of the covalent dimers with the target HMGB1 protein and their *in vitro* activity were tested.

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OP6

EXPLORING THE G-QUADRUPLEX/I-MOTIF CO-LOCALIZATION WITHIN A B-DNA CONTEXT

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DNA can fold into variable arrangements which are expected to exploit regulatory functions. Genome sites enriched in guanines are prone to fold into G-quadruplexes (G4) while the complementary strands fit with i-Motifs (iM) formation [1]. Genome-wide analysis confirmed their formation although with a differential distribution along the cell-cycle stages [2], in accordance with a model that indicates steric hindrance as the main factor to prevent their simultaneous presence at one site [3]. However, iM have been reported to inhibit G4 extension by telomerase, thus pointing to a functional interplay between these two structures [4]. In this work, we started with a double-stranded construct where two lateral duplexes flank a central G/C rich region. Here, the non-canonical structures can form only when the duplex is destabilized. While in cell this physiologically occurs [5], for our in vitro studies we designed two not fully complementary G4 and iM forming sequences. Through an extensive biophysical characterization of different constructs, we proved that G4 and iM structures can be accommodated at the same time. A complete thermodynamic characterization of our construct unravelled the complex equilibria connected to the simultaneous folding in G4/iM of a genomic domain. Our findings shed light on an unripe issue, suggesting that the concomitant formation may play a role in fine-tuning complex biological mechanisms.

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OP7

A SAXS-GUIDED EXTREMELY COARSE-GRAINED MONTE CARLO SIMULATION APPROACH TO INVESTIGATE G4 MULTIMERIC STRUCTURES

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Since G-Quadruplexes (G4s) emerged as a promising research topic due to their potential biological significance and therapeutic applications, most studies have focused on elucidating their properties in the monomeric state. However, understanding the mechanisms by which multiple G4 units interact with each other may also be crucial for uncovering how these structures behave closer to physiological conditions [1]. Within this context, Small Angle X-ray Scattering (SAXS) stands out as a powerful technique with the adequate spatial resolution to access relevant information about inter-G4 correlations [2]. Therefore, we developed a SAXS-guided Extremely Coarse Grained (ECG) Monte-Carlo Simulation method. Our approach was effectively employed to characterize the self-assembly of single G4 units through stacking interactions, allowing us to estimate the degree of multimerization and its correlation with the specific G4 topology [3, 4]. The effect of ligand binding was also investigated. Subsequently, we applied the same method to study long telomeric sequences, which are able to form multiple G4 domains separated by TTA linkers. We found that our approach is able to assess the effect of inter-G4 stacking interactions on the flexibility of these multimeric structures [3]. We also propose a helix-coil model to analytically describe the stacking-unstacking equilibrium within G4 multimers and predict the occurrence of stacked and unstacked G4 multiplets in arbitrarily long sequences.

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OP8

USE OF CHEMOMETRICS FOR EXTRACTING HIDDEN INFORMATION FROM SPECTROSCOPIC DATA

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Chemometrics is a multidisciplinary field that uses mathematical and statistical methods to extract hidden information from any kind of data. The aim of chemometrics is to develop models that can accurately predict or classify samples based on their chemical or physical properties. This approach has been widely applied in various fields of chemistry, such as environmental monitoring, drug discovery, and food analysis. The use of chemometrics allows for the identification of patterns and correlations that may not be easily observable by traditional methods. Indeed, chemometric models are capable of handling large and complex datasets, making it possible to analyze multiple variables simultaneously by reducing the dimensionality of the data and simplifying the interpretation of the results.

One of the most common applications of chemometrics is in spectroscopic analysis. In particular, spectroscopic data can be analyzed using chemometric techniques such as principal component analysis (PCA) and multivariate curve resolution (MCR) to extract information about peculiar features of the samples being analyzed. During this communication, examples of applications of such techniques to various kind of spectral data originating from non-canonical DNA samples will be provided.

OP9

SOLVENT-DRIVEN STRUCTURAL MODULATION OF DIPHENYLALANINE ASSEMBLIES REVEALED BY MICRO-FTIR IMAGING

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Diphenylalanine (FF) has attracted considerable attention in recent years due to its remarkable ability to self-assemble into a variety of nanostructures such as nanotubes, fibrils, and crystals. These assemblies are of particular interest for biomedical applications - especially as antibacterial agents - owing to their intrinsic biocompatibility, mechanical robustness, and capacity to disrupt bacterial membranes. [1,2] FF-based materials have also demonstrated promise in drug delivery, biosensing, and tissue engineering scaffolds, where precise molecular-level organization is critical to their function. [3,4]
In this study, we investigated FF self-assemblies formed in three different solvent environments: ultrapure water, 20% ethanol in water, and 20% dimethyl sulfoxide (DMSO) in water. These systems were selected to explore how solvent polarity and hydrogen-bonding capabilities modulate the structural organization and chemical microenvironment of the FF assemblies. To probe both chemical composition and spatial organization of the assemblies, we employed micro-Fourier Transform Infrared (micro-FTIR) imaging, a vibrational spectroscopic technique that enables simultaneous acquisition of molecular fingerprint information and spatially resolved chemical maps. This label-free approach allows direct correlation between chemical features and morphological structures in peptide-based materials. To complement the spectroscopic analysis, scanning electron microscopy (SEM) was used to directly visualize the morphology and surface features of the assemblies, revealing significant variations in shape and dimensionality depending on the solvent system. Together, these multimodal approaches provide a comprehensive view of how solvent environment governs the formation, structure, and spatial arrangement of diphenylalanine-based nanostructures. Our findings contribute to the broader effort of designing functionally optimized biomaterials by tuning their molecular environment.

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OP10

ELECTRIC FIELD OF DNA IN SOLUTION: WHO IS IN CHARGE?

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In solution, DNA, the "most important molecule of life," is a highly charged macromolecule that bears a unit of negative charge on each phosphate of its sugar-phosphate backbone. Although partially compensated by counterions (cations of the solution) adsorbed at or condensed near it, DNA still produces a substantial electric field in its vicinity, which is screened by buffer electrolytes at longer distances from the DNA. This electric field is experienced by any charged or dipolar species approaching and interacting with the DNA. So far, such a field has been explored predominantly within the scope of a primitive model of the electrolytic solution, not considering more complicated structural effects of the water solvent.

In this work [1], we investigated the distribution of the electric field around DNA using linear response nonlocal electrostatic theory [2], applied here for helix-specific charge distributions, and compare the predictions of such a theory with fully atomistic, large-scale, molecular dynamics simulations. Both approaches are applied to unravel the role of the structure of water at close distances to and within the grooves of a DNA molecule in the formation of the electric field. As predicted by the theory and reported by the simulations, the main finding of this study is that oscillations in the electrostatic potential distribution are present around DNA, caused by the overscreening effect of structured water [3]. Surprisingly, electrolyte ions at physiological concentrations do not strongly disrupt these oscillations and are rather distributed according to these oscillating patterns, indicating that water structural effects dominate the short-range electrostatics. We also showed that (i) structured water adsorbed in the grooves of DNA leads to a positive electrostatic potential core relative to the bulk, (ii) the Debye length some 10 Å away from the DNA surface is reduced, effectively renormalised by the helical pitch of the DNA molecule, and (iii) Lorentzian contributions to the nonlocal dielectric function of water, effectively reducing the dielectric constant close to the DNA surface, enhance the overall electric field. The impressive agreement between the atomistic simulations and the developed theory substantiates the use of nonlocal electrostatics when considering solvent effects in molecular processes in biology.

When considering two DNA molecules in solution, water structure is shown to overall enhance their electrostatic interaction [4, 5], further substantiating the physical theories of sequence homology recognition, a vital precursory step for DNA repair and replication processes.

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OP11

BROWNIAN DYNAMICS OF DISORDERED PROTEINS IN NANOCONFINED ENVIRONMENTS

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Brownian motion of protein molecules in confined environments is fundamental for elucidating their behavior and function at the molecular level [1]. In this study, we investigate the dynamics of intrinsically disordered protein molecules (Aβ-42) under nanoconfinement using Liquid Transmission Electron Microscopy (LTEM) [2,3], a technique that enables high-resolution imaging in liquid environments. Leveraging LTEM, we track the real-time motion of individual protein monomers, oligomers, and fibers with nanometer spatial resolution. The proteins are confined within an ultra-thin liquid layer sealed between two electron-transparent membranes. Our observations reveal anomalous diffusion behavior of the proteins under confinement. To further characterize the mechanical properties of protein oligomers, we developed a high-throughput flicker spectroscopy pipeline [4,5] for analyzing shape fluctuations, enabling quantification of interfacial tension and bending rigidity. Our results demonstrate that protein oligomers exhibit soft and flexible behavior, a property that likely facilitates their interactions with fibrils during secondary nucleation. This work highlights the importance of probing the dynamics of proteins at the nanoscale, providing critical insights into the fundamental processes underlying protein aggregation, function, and misfolding-related diseases.

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OP12

INFLUENCE OF PHOTOACTIVATED WATER ON THE PHYSICO-CHEMICAL PROPERTIES OF COSMETIC INGREDIENTS

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Alzheimer's disease is characterized by extracellular deposits of amyloid beta (Aβ) peptides, a hallmark strongly linked to neurodegeneration. These intrinsically disordered proteins (IDPs) exhibit flexible conformations that enable them to self-assemble into various aggregates, with smaller oligomers often implicated as particularly toxic [1]. Among the major isoforms, Aβ40 and Aβ42 differ by just two residues but display distinct aggregation patterns, with Aβ42 forming oligomers and fibrils more rapidly and potently. Secondary nucleation on preexisting fibrils, whereby surfaces catalyze the formation of new oligomers, further accelerates aggregate proliferation [2]. Understanding these early misfolding processes in both Aβ40 and Aβ42 is crucial for designing interventions aimed at mitigating oligomer toxicity and disease progression. Liquid-phase transmission electron microscopy (TEM) enables real-time imaging of protein aggregation under near-physiological conditions, avoiding the vacuum and freezing requirements of conventional EM [3]. By enclosing the sample between thin silicon nitride membranes, we maintain a hydrated environment that captures dynamic processes in situ. To gain a residue-level perspective on the molecular mechanisms involved, we integrate liquid-phase TEM data with molecular dynamics (MD) simulations, providing a robust approach for investigating misfolded proteins.
In this work, we combined liquid-phase transmission electron microscopy (TEM) with molecular dynamics (MD) simulations to investigate the misfolding behavior of amyloid beta (Aβ) peptides. Using liquid-phase TEM, we observed monomers present on fibril surfaces, ongoing fibril elongation, and new fibril formation. In parallel, our MD simulations on Aβ(1-40) and Aβ(1-42) monomers binding to fibrils showed that Aβ(1-42) monomer-fibril stays attached for longer periods than Aβ(1-40) and more readily triggers secondary nucleation. Analysis of residue-residue contacts indicated that the extra C-terminal residues in Aβ(1-42) stabilize interactions with the fibril, speeding up fibril growth. We also simulated multiple Aβ(1-42) monomers in solution, which aggregated into small oligomers (dimers and tetramers) with radii of gyration around 2-3 nm, an observation consistent with our imaging results. Together, these data support the idea that Aβ(1-42) drives faster aggregation than Aβ(1-40) through secondary nucleation and demonstrate how combining real-time TEM imaging with MD simulations can deepen our
understanding of misfolded protein dynamics.

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OP13

PH-INDUCED CONFORMATIONAL TRANSITION IN REGENERATED SILK FIBROIN AND ITS APPLICATION TO BIO-BASED 3D PRINTING

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Materials based on silk fibroin (SF), a protein extracted from *Bombyx mori* cocoons, have a wide range of applications, from textile industry to biomedical engineering and microelectronics. These applications are enabled by the ability to control the behaviour of the molecule in response of environmental conditions or external stimuli. In this study, we used infrared and Raman techniques to show that SF films obtained through a regeneration process involving formic acid and calcium chloride (pH 4) undergo a conformational transition from a more amorphous/β-turn-like structure (Silk I) to a more crystalline/β-sheet-like structure (Silk II) when redissolved in phosphate-buffered saline (PBS, pH 7.4). Moreover, ultrasonic bath treatment of the silk solution in PBS facilitates the transition towards Silk II, while it does not affect the formic acid solution. The conformation of the dissolved protein in response to pH variations and ultrasonic treatment was then analyzed using circular dichroism.
From an application perspective, the piezoelectric properties of the Silk II structure combined with the presence of Ca^{2+} ions, have been exploited to realize an extrusion-based 3D printed self-powered memristor, capable of switching from low resistance to high resistance state that recovers in a few minutes, mimicking a transient memory.

PROBING WATER ORDERING IN LIQUID-LIQUID PHASE SEPARATION PHENOMENA

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Liquid-liquid phase separation (LLPS) is a fundamental physicochemical phenomenon whereby a homogeneous solution, under specific conditions, separates into two distinct phases: a protein-rich (concentrated) phase and a protein-depleted (diluted) phase. LLPS has emerged as a crucial mechanism in many biological systems due to its involvement in the formation of the membrane-less organelles, cellular compartments not bound by membranes [1]. LLPS implies a delicate balance between enthalpic and entropic contributions, with protein-protein and protein-solvent interactions playing a pivotal role. In particular, the role of solvent is recognized as crucial in orchestrating phase separation, although it remains challenging to elucidate [2]. Moreover, environmental factors, including temperature, pH, and solute concentrations, critically influence these interactions and thus the whole phase separation process. The analysis of LLPS in solutions containing model proteins may provide insight into these intricate mechanisms.

Here we present an experimental study on the LLPS of an aqueous solution of Bovine Serum Albumin (BSA) and Poly-Ethylene Glycol (PEG) as a model system to investigate the role of water ordering on LLPS and how water ordering is influenced by the phase transition. The system was characterised by means of turbidity measurements, steady-state fluorescence spectroscopy, two-photon microscopy, Fluorescence Lifetime Imaging Microscopy (FLIM) and X-Ray Photon Correlation Spectroscopy (XPCS). Results highlight that the solution is homogeneous at high temperature and undergoes a reversible LLPS upon temperature decrease. The use of 6-acetyl-2-dimethylaminonaphthalene (ACDAN), a fluorescent dye highly sensitive to water dipolar relaxation [3], was crucial to explore the water ordering upon LLPS. ACDAN fluorescence measurements revealed an overall increase in water ordering associated with the phase transition.

Additionally, the introduction of chaotropic and kosmotropic agents into the system allowed for a deeper investigation of the role of water structuring. XPCS measurements performed at the ESRF showed that these agents respectively increase and decrease the transition temperature, highlighting the critical role of the water hydrogen-bond network in LLPS phenomena.

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POSTER PRESENTATIONS

PP1

AI-POWERED PEPTIDE DESIGN FOR MEMBRANE FUNCTIONALIZATION

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The application of Artificial Intelligence (AI) tools in peptide and protein design has greatly advanced the development of biomolecules with tailored molecular functions, impacting fields such as diagnostics, medicine, and materials science [1]. Driven by AI's potential in life sciences, this work applies Deep Learning (DL) to design novel antimicrobial peptides, validate their activity in wet-lab experiments, and immobilize the most effective on Nylon 6,6 to create antimicrobial filter membranes.
Two DL algorithms, HydrAMP and Amplify, were used to design and select three peptide sequences - AMP1, AMP2, and AMP3 – with *in silico* predicted antimicrobial activity [2,3]. Wet-lab studies validated these predictions by testing the peptides' antibacterial effectiveness against different bacterial strains. AMP3 emerged as the most active, particularly against *E. coli*.
A detailed biophysical characterization of AMP3 on model membranes - using differential scanning calorimetry, circular dichroism, and fluorescence spectroscopy - revealed that its efficacy relies on its ability to integrate efficiently into lipid bilayers [4].
To evaluate AMP3 in real-world application, it was immobilized on Nylon membranes following a *grafting-through strategy*. Detailed physicochemical analyses, including DSC, WAXS, and UV-Vis spectroscopy, confirmed successful incorporation without altering the semi-crystalline structure of Nylon 6,6. Peptide-Nylon membranes were then produced using electrospinning and phase inversion methods. Interestingly, the peptide-membrane composites, when assayed for activity against *E. coli*, led to a significant reduction in bacterial viability.
In conclusion, the combined approach of computational prediction and experimental implementation enabled the construction of multifunctional materials with promising applications across various fields such as water filtration and purification [5].

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MACHINE LEARNING-DRIVEN MD SIMULATIONS REVEAL THERMAL TUNING OF PROTEIN HYDRATION IN A HYPERTHERMOPHILIC ENZYME

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Proteins are intricate biological entities that serve as fundamental components for the proper functioning of living organisms. As proteins operate in aqueous environment, water molecules at the protein interface can actively participate in functional processes, ranging from protein structure stabilization to the modulation of protein-protein and protein-ligand interactions [1-4]. Moreover, several studies have suggested a connection between protein dynamics and the behavior of their hydration shells [5-7]. Studying hydration dynamics at the protein interface is therefore crucial to understanding protein functional mechanisms, especially in extreme environments. An interesting case is represented by waters surrounding proteins from hyperthermophilic organisms, which are capable of maintaining structure and dynamics similar to their mesophilic homologues, despite large differences in physiological temperature and the kinetic properties of bulk water [8]. In this study, we investigated protein hydration at high temperature by performing molecular dynamics (MD) simulations of two homologous acylphosphatase enzymes: one mesophilic active at 37°C, and the other hyperthermophilic, active at 80°C. Conventional protein force-fields are not parametrized to reproduce protein behaviour at high temperature, often leading to inaccurate results. To overcome these limitations, MD simulations were restrained with experimental NMR chemical shifts (CSs) using NapShift [9], a machine learning model we previously developed to predict CSs from protein structure and integrate them as derivatives in biomolecular simulations, improving the accuracy of the underlying force fields. Analysis of the structural and dynamical properties of waters at the surface of the two enzymes revealed comparable first hydration shells, including solvent molecules near the active sites, though with reduced water population at higher temperature. In contrast, major differences were observed for waters residing in the second hydration shell, showing markedly enhanced mobility in the hyperthermophilic enzyme [10]. This work demonstrates how machine learning-driven MD simulations provide more accurate modeling of protein-water interactions and reveal subtle but relevant differences in protein hydration across temperatures, suggesting a thermally tuned hydration environment beyond the immediate protein interface.

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UNRAVELING THE IMPACT OF LIGAND BINDING IN CANCER THERAPY: A COMPARATIVE MOLECULAR DYNAMICS STUDY OF FREE AND LIGAND-BOUND G-QUADRUPLEXES

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G-quadruplexes (G4s) are non-canonical secondary structures of nucleic acids that form in guanine-rich regions of the genome. Among the best-characterized G4s are those located at telomeres - the repetitive terminal sequences of linear chromosomes - which have emerged as crucial regulators of genome stability and cellular proliferation. In particular, telomeric G4s are known to modulate the access of telomerase, an enzyme aberrantly reactivated in the majority of cancer cells, thereby making these structures attractive targets for therapeutic intervention.
The human telomeric sequence, often studied in its 22-nucleotide form (Tel22), can adopt multiple topological conformations - parallel, antiparallel, and hybrid - depending on the ionic environment and molecular crowding conditions. Several small molecules, known as G4 ligands, have been developed to selectively bind and stabilize these structures, especially with the aim of inhibiting telomerase activity. However, a detailed atomistic understanding of how ligand binding affects G4 the mechanism of unfolding and the switching between distinct G4 conformers under physiological conditions is still incomplete.
In this study, we employ all-atom molecular dynamics simulations to investigate possible changes in the structural and hydration properties of Tel22 parallel conformation upon binding to berberine (a known G4 ligand), and switching to an antiparallel conformation [1]. We observe that both perturbations induce a slight increase in Tel22 compactness and structural fluctuations. The higher compactness of the parallel G4 bound to berberine with respect to the ligand-free parallel structure suggests a stabilizing effect of the ligand, consistent with the proposed mechanism of action. The increased conformational flexibility in the presence of the ligand is in agreement with previous neutron scattering findings [2]. Despite these differences, the average hydration levels of the three systems remain comparable, suggesting that global solvent accessibility is not markedly altered.
To gain deeper insight into the large-scale motions underlying G4 dynamics, we applied essential dynamics (ED) analysis to these trajectories. This approach allowed us to identify the dominant collective motions of the system and characterize how ligand binding affects conformational flexibility. Ultimately, our goal is to use ED results as a starting point to explore the molecular mechanisms of thermal conformational interconversion, and ligand binding.

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MOLECULAR INSIGHTS INTO LIGNIN DERIVATIVE INTERACTIONS IN WATER FOR SUSTAINABLE SKIN-DELIVERY SYSTEMS: QUANTUM CHEMICAL PERSPECTIVES

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Lignin is one of the most abundant natural biopolymers and plays a vital role in developing safe and sustainable alternatives for healthcare products. In this study, we investigated the interactions between lignin bipolymer models essential for delivering therapeutic and cosmetic compounds. Using quantum chemistry calculations with various theoretical approaches such as DFT and TDDFT, we examined aspects like antioxidant mechanisms and the electronic properties of lignin derivatives. These findings offer valuable insights into the molecular mechanisms governing the interactions between lignin derivatives in aqueous environments, which has im-plications for creating bio-based skincare formulations and transdermal delivery systems. Our results emphasize the significance of molecular size in optimizing lignin-derived compounds for dermatological applications.

COMPUTATIONAL DESIGN OF POLYMER-BASED NANOPLATFORMS FOR ADVANCED GENE AND DRUG DELIVERY SYSTEMS

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Recent advancements in gene therapy have opened the door to a new wave of treatments, laying the groundwork for next-generation technologies. A key challenge in gene therapy is the development of effective gene delivery systems. Natural and synthetic macromolecules, with their versatility as building blocks in soft nanotechnology, play a central role in the creation of specialized delivery vectors with tailored compositions and functions. In this work, we introduce an innovative computational approach to precisely optimize polymers and/or nanocomposite architectures as efficient components for polymer-based nanoplatforms. By integrating cutting-edge artificial intelligence techniques with advanced modeling methods, we present an adaptive design strategy for these nanoplatforms. This synergistic approach demonstrates how computational modeling can accelerate the discovery of novel delivery vectors, unlocking new possibilities for technological applications in gene therapy.

DEVELOP NEXT GENERATION ATOMISTIC FORCE FIELD TO INVESTIGATE PROTEINS IN SALTY SOLUTIONS

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Complex liquids and biomolecular systems exhibit correlations spanning multiple length and timescales, influencing key physical chemistry phenomena such as cosolvation, cononsolvation, hydrotropy, collapse, and folding. Molecular dynamics (MD) simulations with atomistic, empirical potential energy functions provide a powerful tool to investigate these effects, but their accuracy and transferability remain challenges.

While existing water force fields effectively reproduce water-water interactions, current ion force fields struggle to capture the properties of hypersaline solutions due to their optimization in dilute conditions. This limitation is particularly relevant for the study of halophilic proteins, which thrive in multi-molar KCl environments by exhibiting more acidic and polar amino acids, fewer hydrophobic and cationic residues, and unique solvation properties essential for their stability and function [1-2]. Our work focuses on developing next-generation force fields of intermediate complexity to improve the accuracy of simulated observables and extend applicability across diverse aqueous environments. Optimizing force fields for molar electrolyte solutions is crucial for accurately describing the solvation shell of halophilic proteins, ultimately advancing our understanding of biomolecular stability in extreme conditions.

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PP7

DESIGNING *DE NOVO* AMYLOID FIBRILS AS A PLATFORM FOR SUSTAINABLE BIONANOMATERIALS

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The pressing environmental and technological challenges of our time demand the development of innovative and sustainable biomaterials. Among the most promising candidates are amyloid fibrils, highly ordered protein assemblies formed by the self-assembly of peptides. These nanostructures typically exhibit β-sheet-rich architectures, where individual strands align perpendicularly to the fibril axis to form densely packed, hydrogen-bonded cross-β structures [1]. Although historically associated with neurodegenerative diseases, amyloid fibrils are increasingly recognized for their exceptional robustness, biocompatibility, and modularity, making them attractive building blocks for a wide range of functional bionanomaterials [2-4]. This research project aims to design *de novo* peptide sequences that can form stable, non-pathogenic amyloid fibrils with tunable properties. The goal is to establish a computational framework for the rational and generative design of synthetic fibrillar materials, enabling fine control over structural features and functionality at the nanoscale. These artificial fibrils have the potential to serve as sustainable nanomaterials in diverse applications, including biosensing, nanotechnology, and environmental remediation [5,6]. Among these, water remediation stands out as a particularly promising application of such nanomaterials [7,8]. The early stage of this work is focused on constructing a curated dataset of natural amyloid-forming sequences and structures to extract fundamental sequence-structure principles. These insights will inform the training of generative deep learning models capable of proposing novel sequences with high assembly potential and tailored physicochemical properties. By integrating computational protein design with concepts from biophysics, this project seeks to open new avenues in the bottom-up design of programmable biomaterials for next-generation sustainable technologies.

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PP8

FLUORESCENCE-BASED INVESTIGATION OF WATER NETWORK USING ACDAN DYE

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The structural organization and interactions of water molecules are fundamental to numerous physical, chemical, and biological processes. Water's capacity to form hydrogen bonds (H-bonds) is key to its exceptional properties and allows it to adapt dynamically to changes in its surroundings. These molecular-level interactions influence critical phenomena such as protein folding, enzymatic function, and cellular architecture. In biological systems, the H-bonding network of water can be significantly modified by the presence of solutes and spatial confinement.

Here, we investigated the fluorescence emission of 2-acetyl-6-(dimethylamino) naphthalene (ACDAN) in aqueous solutions containing kosmotropic and chaotropic salts, as well as in agar-based hydrogels [1]. ACDAN has recently emerged as a powerful probe for exploring the structure and dynamics of water networks, as its fluorescence is sensitive to the local dielectric environment and reflects changes in water dipolar relaxation. Our findings demonstrate that the spectral behaviour of ACDAN correlates with the degree of water structuring, offering valuable insights into solute–water interactions and water behaviour in both free and confined conditions.

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THE ROLE OF MOLECULAR CROWDING IN G-QUADRUPLEX ASSEMBLY BY COARSE-GRAINED MODELING: IMPLICATION FOR ANTICANCER DRUGS

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G-Quadruplexes (G4) are non-canonical secondary structures formed by G-rich sequences of DNA or RNA, capable of adopting diverse conformations that influence critical biological processes. Human telomeric regions, which can extend up to 25 kb, are particularly prone to forming multimeric G4 assemblies. Emerging evidence suggests that G4 structures not only preserve genomic integrity but are also implicated in the progression of severe pathologies, including 85-90% of cancers and various neurodegenerative diseases. This has positioned G4 as highly promising targets for novel anticancer therapeutics. However, challenges remain in understanding their conformational stability and interactions with external molecules, limiting the effectiveness of G4-based therapeutic strategies.

In this work we apply coarse-grained molecular dynamics (MD) simulations to investigate the folding and unfolding dynamics of multimeric G4 structures under physiologically relevant crowded environments.

To achieve this, we developed a new coarse-grained model in which the basic unit is a single deoxyguanosine, represented as a 3 × 2 grid of equidistant spheres. Different units are linked together by a suitable interaction potential and the resulting filament can fold into the desired G4 secondary structure through hydrogen bonding between deoxyguanosines, modeled using the Lennard-Jones potential to form G4 tetrads. To mimic stacking interactions between monomers, each composed of three tetrads, the center-of-mass (CoM) particles of the outer G-tetrads are subject to a central attraction, also modeled via the Lennard-Jones potential.

We used this model to study the properties of G-quadruplex multimers, both in the presence and absence of crowder molecules, to mimic in vivo conditions. Simulation data are compared with experimental SAXS measurements [1] and outcomes from alternative models [2] at different scales. This allowed us to validate our model and exploit its potential to study the mechanisms of G4 unfolding. We plan to use this model to further investigate the folding/unfolding pathways and aggregation kinetics of G4s, both with and without ligand molecules.

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EXTREMELY COARSE-GRAINED MONTE CARLO SIMULATIONS FOR INTERPRETING SAXS DATA OF NUCLEIC ACID STRUCTURES

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We present a general framework based on coarse-grained (CG) and extremely coarse-grained (ECG) Monte Carlo simulations, developed to interpret small-angle X-ray scattering (SAXS) data from nucleic acid systems. The approach starts with experimental SAXS measurements and proceeds through a parameter-optimized simulation scheme, in which biomolecular components are represented as rigid elements (spheres, cylinders, or more complex shapes) with patch-based interactions. The level of coarse-graining can be adapted to the system under investigation: in ECG models, an entire structural unit - such as a G-quadruplex - is represented by a single element, while in standard CG models, higher resolution is achieved by representing individual components (e.g., single nucleotides) separately to account for intra-molecular flexibility. By tuning geometrical and energetic parameters to match the experimental scattering profile, the model bridges SAXS observables with microscopic structural features that are otherwise inaccessible—such as persistence length and stacking forces.

We first applied the ECG methodology to study G-quadruplex (GQ) multimers formed by telomeric sequences [1]. Each GQ unit is modeled as a hard cylinder connected by directional patches representing TTA linkers and stacking interactions. The optimal cylinder dimensions were selected to best reproduce the experimental structure factor across different ligand concentrations. Once validated, the model was used to extract stacking energies and multimer length distributions, providing insights into how ligands modulate GQ stacking and the thermodynamics of telomeric DNA assembly.

We then developed a CG model for single- and double-stranded DNA [2], modeling each nucleotide as a cylindrical element with directional patches for stacking and base pairing. The resulting models successfully reproduce SAXS data and allow for the extraction of key structural parameters, including persistence length and end-to-end distance.

This SAXS-guided modeling framework is broadly applicable to a variety of biomolecular systems and offers a powerful, flexible tool for extracting structural information from scattering experiments.

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PP11

DIRECT OBSERVATION OF HYDRATION WATER IN PROTEINS USING RAMAN SPECTROSCOPY

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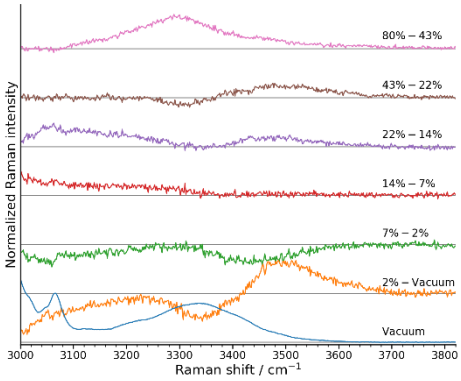
For synthetic polymers, hydration water critically influences both mechanical and chemical properties, such as viscoelasticity and biocompatibility. It is typically classified into non-freezing bound water, which is strongly bound and has reduced mobility, and freezing bound water, which is more mobile. Recently, a third type - intermediate bound water - has also been identified, showing properties between the two types. Intermediate water plays a key role in suppressing protein and cell adsorption and is fundamental to biocompatibility [1]. Proteins also possess intermediate water, important for maintaining structural stability and functional activity. However, its regulatory mechanisms remain unclear. A major reason for this is that there are limited techniques available to distinguish among these water types, making it difficult to obtain structural and bonding information. To address this problem, we employed Raman spectroscopy, which analyzes structures and hydrogen bonding interactions of water, and successfully monitored the hydration process of vacuum-dried proteins.

The intrinsically disordered protein FUS LC was vacuum-dried and exposed to nitrogen gas with controlled relative humidity (RH) to induce hydration. Raman spectra were recorded at each RH level using a homemade inverted confocal Raman microscope [2]. The changes in the intensity and shape of the O-H stretching vibration band were analyzed (Figure). Under vacuum conditions prior to hydration, a band with a peak around 3350 cm^{-1} was observed, attributed to hydroxyl and amino groups of FUS LC. Upon exposure to nitrogen at 2% RH, a new component with a peak around 3500 cm^{-1} emerged and increased up to 43% RH. At 80% RH, a second component with a peak around 3300 cm^{-1} became prominent. The clear difference in peak wavenumbers indicates that two types of hydration water with distinct adsorption modes were clearly detected.



Raman spectrum of dried FUS LC protein (blue) and spectral changes at each RH during hydration (orange to pink).

Based on these results, combining Raman spectroscopy with quantum chemical and molecular dynamics simulations will enable the elucidation of hydrogen bonding within each hydration water component and its interaction with the protein. This study opens new ways for understanding how different types of hydration water contribute to the structural stability and functional regulation of proteins.

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TUTORIALS

TU1
PHOBIC AND PHILIC: HYDROPHOBIC INTERACTIONS AND WETTING TRANSITIONS
K. Koga

TU2
RAMAN BANDS OF WATER: QUANTIFYING WATER DENSITY AND BIOMOLECULES IN A LIQUID DROPLET AND A LIVING CELL
T. Nakabayashi

TU3
NANOCONFINED WATER: UNLOCKING RECONFIGURABLE STRUCTURES BEYOND BIOLOGICAL LIMITS
X. Chen

TU4
HARNESSING DEEP LEARNING FOR ANTIMICROBIAL PEPTIDE DESIGN
A. De Simone

TU5
THE ROLE OF WATER IN PROTEIN FOLDING
A. Pastore

TU6
ANALYZING STRUCTURAL PROPERTIES OF WATER (AND OTHER MOLECULES) WITH AI/ML
M. Kartunnen

PLENARY LECTURES

PL1
SYNERGISTIC SOLVENT EFFECTS ON THE STRUCTURE AND MECHANICS OF LIPID MEMBRANES
P. Sassi

PL2
STRUCTURE-DEPENDENT HYDRATION AND PHASE SEPARATION OF NUCLEIC ACIDS
D. Miyoshi

INVITED LECTURES

IL1
THE STATE OF WATER UNDER CONFINEMENT AND AT SUBZERO TEMPERATURES
Y. Yao

IL2
REVEALING PROTEIN ASSOCIATION THROUGH COUPLED FLUORESCENCE SPECTROSCOPY AND MICROSCOPY
V. Vetri

IL3
PROTEOME DYNAMICS AT THE CELL-DEATH TEMPERATURE: A PICTURE OF LIFE ADAPTATION TO DIFFERENT THERMAL NICHES
F. Sterpone

IL4
THERAPEUTIC POTENTIAL OF CATIONIC AMPHIPHILIC G4 LIGANDS IN CANCER TREATMENT
M. Djavaheri-Mergny

IL5
NON-CANONICAL NUCLEIC ACID STRUCTURES: FROM BIOPHYSICAL CHARACTERIZATION TO PERSONALIZED MEDICINE
J. Amato

IL6
EXPLORING THE UNFOLDING MECHANISMS OF DNA G-QUADRUPLEXES INDUCED BY TEMPERATURE USING 2D UV RESONANT RAMAN SPECTROSCOPY
S. Di Fonzo

IL7
SELF-ASSEMBLED NANOPARTICLES FOR PHOTOINDUCED THERAPIES AND ENERGY HARVESTING
M. Di Donato

IL8
QUADRUPLEXES ARE EVERYWHERE!
J.L. Mergny

IL9
BIOPHYSICAL INSIGHTS INTO COMPLEX FOLDING/UNFOLDING PATHWAYS OF G-QUADRUPLEXES
L. Petraccone

IL10
USING ENTROPY TO CONTROL PHASE SEPARATION IN ASSOCIATIVE POLYMERS
L. Rovigatti

IL11
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