Conference on Frontiers in Atomistic Simulations: from Physics to Chemistry and Biology | (SMR 4098)

08 Sep 2025 - 12 Sep 2025
ICTP, Trieste, Italy

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P01

Ab-Initio Studies of Octahedral Clusters as Building Blocks for Pb-Free Hybrid Perovskites in Photocatalysis and Photovoltaic Applications

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Abstract

Lead-based hybrid perovskites, despite their outstanding optoelecetronic performance, suffer from serious drawbacks due to the toxicity and instability of Pb^{2+} [1,2]. These limitations hinder their large-scale adoption and raise significant sustainability issues for future clean energy technologies. There is, therefore the need to identify and develop Pb^{2+}-free alternatives that retain the desirable properties of traditional perovskites while eliminating the associated risks [3]. In this study, the cluster-based hybrid perovskites $Cs(Nb_6Cl_{12})Cl_3$ and $C_2NH_8(Re_6Se_8)Cl_3$ featuring $Nb_6Cl_{12}^{2+}$ and $Re_6Se_8^{2+}$ clusters, are investigated using density functional theory with the Perdew, Burke, and Ernzerhof functional optimized for solids (PBEsol) within the generalized gradient approximation (GGA) [4]. Electronic structure calculations reveal that both materials are semiconductors with calculated band gaps of 1.20 eV and 1.69 eV, respectively, making them promising candidates for solar energy conversion. The respective formation energies are found to be -8.432 eV and -11.2 eV, indicating that the compounds are thermodynamically stable. Detailed band structure analysis show that the flat-band character is predominantly governed by the d-orbitals of Nb and Re atoms, influencing charge transport and optical absorption properties. The results suggest that the octahedral metal-halide and metal-chalcogen cluster cores can serve as viable alternatives to toxic Pb^{2+} in perovskite materials, offering a pathway toward environmentally safe and highly stable hybrid perovskites for optoelectronic and photocatalytic applications.

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P02

Multiscale Modeling of Catalytic Ethylene Oligomerization in Metal-organic Frameworks

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Single-site catalysts (SAC) combine the easy separation and durability of heterogeneous systems with the activity and selectivity of homogeneous ones [1]. Metal–organic frameworks (MOFs) are outstanding SAC supports because their composition, surface area, acidity and thermal stability are readily tuned [2]. Confinement within MOF pores isolates and stabilizes atomic sites, sharpening selectivity [3]. Ethylene oligomerization illustrates these benefits: porous MOF-based SAC markedly boost activity and control product distribution[4, 5].

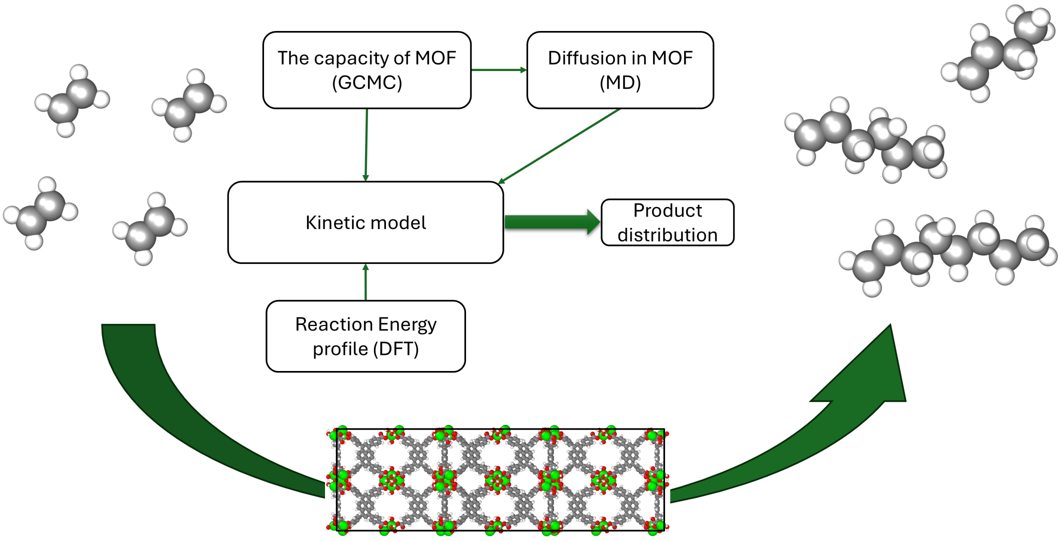

Figure 1: The schematic representation of the multiscale simulation of ethylene oligomerization in NU-1000.

Although metal reactivity is governed by the local electronic structure, probing how MOF confinement changes SAC selectivity, kinetics, and separations requires scale-bridging models that merge reaction energetics with diffusion and pore topology. In our work, we focused on functionalized NU-1000; its hierarchical micro-/mesopores afford selective adsorption and fast diffusion, suiting ethylene oligomerization.

We have created a multiscale kinetic model that quantitatively links DFT-derived reaction energetics with all-atom simulation adsorption and diffusion parameters (from grand canonical Monte Carlo and molecular dynamics) to predict product distribution in NU-1000. By bridging electronic structure insights and transport phenomena, it provides a tool for better analysis of MOF-based catalysis.

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P03

Inferring Causality from Molecular Dynamics Simulations

When Simulations Meet Experiments: U2AF2 as a Test Case

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Understanding the conformational behaviour of hybrid proteins, those containing both folded domains and intrinsically disordered regions (IDRs) remains a significant challenge in molecular simulations [1]. U2 small nuclear RNA auxiliary factor 2 (U2AF2), an essential splicing factor, exemplifies such a hybrid architecture, featuring structured RNA recognition motifs connected by flexible IDRs (32 aa) [2]. In this study, we benchmarked a range of allatom and coarse-grained (CG) force fields to assess their ability to accurately model the conformational ensemble of U2AF2. Molecular dynamics (MD) simulations were conducted using multiple force fields, including AMBER [3], MARTINI3-IDP [4] and SIRAH2 [5]. The resulting ensembles were rigorously compared against experimental Förster resonance energy transfer (FRET) and small-angle X-ray scattering (SAXS) data. Our results highlight significant differences in the extent of compaction, domain orientation, and flexibility captured by each force field. While all-atom force fields align well with experimental observations, most CG models tend to overcompact the IDR regions.

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Molecular-Level Mechanistic Insights into PETase-Catalyzed Plastics Hydrolysis from Accurate QM/MM Free Energy Calculations

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The enzyme PETase[1] is capable of depolymerizing plastics such as polyethylene terephthalate (PET) at moderate temperatures, and demonstrated even higher activity towards polyethylene-2,5-furan dicarboxylate (PEF), opening promising routes for the sustainable upcycling of plastic wastes. To fully exploit the potential of these biocatalytic systems, an understanding of the mechanism of their activity at the atomistic level is pivotal.

To this end, this study investigates two fundamental stages of the catalytic cycle of PET and PEF hydrolysis by PETase—acylation and deacylation—using hybrid QM/MM enhanced sampling molecular dynamics simulations to capture all relevant dynamic effects.[2] Well-tempered metadynamics simulations at the DFTB3 level are performed along collective variables optimized via linear discriminant analysis,[3] a supervised learning-assisted approach that accounts for the contributions of each potentially relevant degree of freedom. The free energy (FE) profiles indicate that the acylation stage is the rate-limiting step for both PET and PEF degradation, with barriers ≈ 8 kcal/mol and ≈ 4 kcal/mol higher than those obtained for the deacylation step, respectively. Remarkably, substantial mechanistic differences are found. While PET acylation occurs in a concerted manner, with a single energy barrier of ≈ 21 kcal/mol, PEF acylation follows a two-step mechanism where after the first barrier, ≈ 10 kcal/mol high, a metastable intermediate state is formed, which then evolves towards the product once a second barrier of ≈ 2 kcal/mol is overcome. This mechanistic description is consistent with the FE profiles obtained at higher levels of theory (PBE, B3LYP, RI-MP2) via FE perturbation,[4] thus validating the key insights elucidated by metadynamics simulations. Finally, both global and local reactivity descriptors derived from conceptual density functional theory[5] suggest that PEF is more electrophilic and susceptible to nucleophilic attack than PET. The results obtained by means of the robust computational protocol adopted here offer for the first time thermodynamic and mechanistic insights into PET and PEF hydrolysis by PETase at the molecular level. This work elucidates the experimentally observed enhanced activity of this enzyme toward PEF, paving the way for further exploration of biocatalytic plastic recycling.

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P06

The Interaction of Hydrogen with Iron under High Temperature and Pressure

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Absorbed hydrogen can significantly affect the mechanical behavior of metals and alloys, potentially causing embrittlement and material failure. In iron and steels, gaseous hydrogen forms atomic hydrogen on the surface, which is the precursor to bulk uptake. This interaction is also a crucial yet often overlooked step in Fe-catalyzed processes such as Haber–Bosch ammonia synthesis, Fischer–Tropsch reactions, and pollutant degradation. Most experimental and theoretical studies have been limited to ultra-high vacuum UHV conditions and first-principles DFT characterizations, overlooking the dynamic behavior and complex process interplay that occur under industrially relevant conditions of high pressures and elevated temperatures. Recent *in situ* and *in operando* techniques have made notable progress[1], but a comprehensive, atomistic picture remains elusive.

In this work, we present a detailed investigation of H_2 interacting with Fe(110) under *operando* conditions of high temperature (>400°C) and pressure (150–350 bar). Building on the expertise developed in our group[2-4], we use a machine-learned (ML) potential trained *ad hoc* for this system, using a large set of *ab initio* quality data. In order to maintain constant pressure during the simulation, we implemented a grand canonical (GCMC) scheme, allowing the system to exchange gas molecules with a imaginary reservoir and applying it solely to the gas-phase region, coupled with molecular dynamics (MD) in a hybrid GCMC-MD approach. As a result, the algorithm is effectively working as a pressure controller, enabling a realistic simulation of such hydrogen-rich environment.

Our study, conducted in the context of the Haber–Bosch process, provides key insights into hydrogen adsorption behavior. We obtained quantitative estimates of sticking coefficients, diffusion constants, and activation barriers across the explored pressure and temperature ranges. We determine an equilibrium hydrogen surface coverage of 0.7–0.8 and identify stable adsorption patterns. The hydrogen layer induces surface rigidity, significantly altering the structural response compared to a clean Fe surface. Furthermore, we estimated properties and availability of catalytic sites: a crucial aspect when considering the binding of co-reactants. Our findings reveal how increased pressure, particularly at high temperatures, impacts the hydrogen-surface interaction, and underscore the importance of accounting for hydrogen-rich conditions in heterogeneous catalysis.

By combining ML-based potentials with constant-pressure MD simulations, our approach bridges the gap between the accuracy of *ab initio* modeling and the realistic representation of catalytic processes, offering a powerful tool to understand hydrogen-induced effects and to guide the development of robust Fe-based catalysts and hydrogen-compatible materials.

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Abstract for "Conference on Frontiers in Atomistic Simulations: from Physics to Chemistry and Biology"

Multi-Scale Modeling of Aβ42 Dynamics

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Amyloid-beta (Aβ) peptides, especially Aβ40 and Aβ42, are intrinsically disordered proteins involved in the pathogenesis of Alzheimer's disease, and exhibit markedly different aggregation behavior and toxicity. In this work, we performed atomistic molecular dynamics simulations, enhanced by well-tempered metadynamics, to explore and compare the conformational landscapes of Aβ40 and Aβ42 monomers in aqueous solution.

We computed a range of structural descriptors and used them to partition the conformational space into distinct families using a density-based clustering strategy. Transitions among these families were also investigated to elucidate the interconversion dynamics within the conformational ensemble.

The atomistic results were then employed to guide the refinement of a foldable coarse-grained (CG) model based on the Martini 3 force field. By aligning the CG potential with the atomistic ensemble, our approach enables mesoscale simulations of Aβ misfolding and oligomerization, bridging time and length scales. This work lays the foundation for studying the early stages of aggregation and the interactions of Aβ oligomers with cellular membranes using a transferable and foldable CG model.

Fundings: This work was supported by PRIN 2022 – NeuRaftAmyl.

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P08

In silico study of the effect of asymmetry on extracellular vesicle membranes

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Extracellular vesicles (EVs) are membrane-enclosed nanoparticles carrying proteins and RNAs, playing key roles in intercellular communication processes such as cancer metastasis, microbiota homeostasis, and viral infections. They hold potential for therapeutic, diagnostic, and nutritional applications [1]. Despite growing interest, due to the lack of robust theoretical and simulation tools, our understanding of EVs remains limited, particularly in connecting their molecular composition and structure to mesoscale properties like mechanical behavior and functional aspects such as fusogenicity.

Molecular Dynamics (MD) simulations offer a powerful approach to study the microscopic details of EV membranes and connecting these to their mesoscale properties and mechanisms of action, such as membrane fusion. Yet, the multi-scale nature and biologically relevant timescales of EV processes present challenges for MD studies. To overcome these, we employ atomistic and coarse-grained MD simulations coupled with advanced sampling techniques, enabling *in silico* design of EVs with tailored properties.

We focus on PC-3 prostate cancer-derived EVs to investigate how asymmetric membrane compositions influence their biophysical properties. Using lipidomics-informed models, we simulate membranes with different lipid components, including glycerophospholipids, sphingolipids, phosphatidylcholines, and high percentages of cholesterol [2]. We systematically analyze how asymmetry affects key membrane properties such as phase separation, thickness, and bending rigidity. We also compute free energy barriers of stalk formation, a critical step in membrane fusion, to understand how compositional asymmetry affect EV fusogenicity.

This work has been developed in the framework of the 2022 PRIN-PNRR project v-EV (P2022EKHKL) funded by MUR, Italy.

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Investigation of Monomer Exchange Dynamics in Ureido-Pyrimidinone based Supramolecular Polymers

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The use of synthetic supramolecular polymers (SPs), built by monomers that self-assemble via non-covalent, reversible interactions, is rapidly growing in many fields, including energy, environmental, and bioengineering applications [1,2]. Very recently ureido-pyrimidinone (UPy)-SPs have been used to synthetize biocompatible hydrogels aiming to mimic the dynamic environment of extracellular matrices [3,4]. UPy monomers dimerize by self-complementary quadruple hydrogen bonding in a donor-donor-acceptor-acceptor (DDAA) fashion and these planar dimers are the building blocks of fibrillar stacks, which, in turn, can interact to form more complex polymeric networks in water. Tuning the dynamics, stiffness, and bioactivity of such UPy-based hydrogels effectively influences cellular behaviour and tissue development. However, a complete understanding of UPy-SP dynamics over different length and time scales is still lacking, and even the most advanced experimental approaches are unable to capture the dynamics of monomer exchange with atomistic resolution.

Here we present a computational study on UPy-SPs in water that reveals the mechanism of UPy monomer exchange between UPy-SPs and their surroundings. Our results, based on atomistic Molecular Dynamics (MD) simulations combined with enhanced sampling techniques show that the fine interplay of solute-solvent interactions is the main engine of supramolecular monomer motion in water, thereby making UPy fiber ends more dynamic as compared to static UPy fiber backbone. Then, by combining the τSOAP [5] descriptor with Machine-Learning (ML)-based analysis, we monitor the transition of UPy monomers among diverse dynamics environments within the fiber, thereby highlighting defect formations, single monomer travelling, and self-healing.

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Unsupervised learning high-dimensional distributions and applications to molecular simulations

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We present an overview of recently developed unsupervised and non-parametric estimators for density and its gradient in high-dimensional spaces. These methods leverage the concept of intrinsic data manifold, without explicitly parameterizing it, to achieve implicit dimensional reduction. This reduction, combined with a point-adaptive bandwidth selection, is crucial for mitigating the curse of dimensionality, enabling effective operation in spaces of $O(10–10^2)$ dimensions.

Among the various applications of density estimation, we focus on its powerful role in analyzing high-dimensional distributions through density-based clustering, with application to molecular simulations. We present two applicative cases of this approach: one in the field of biomolecules, where we demonstrate its utility in characterizing the metastable states visited by a large – medically relevant -- peptide during a long unbiased molecular dynamics simulation. The second one in the field of materials, where illustrate how these methods enable "unsupervised classification" and out-of-distribution detection in complex datasets.

P11

Development of a machine learning potential for water confined in carbon nanotubes

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Water is a simple molecule (H_2O) of paramount importance in industrial and biological processes. Despite its molecular simplicity, it exhibits a complex phase diagram and a series of anomalous properties, making water a unique and essential substance [1]. These anomalies are further amplified when water is confined in nanostructured environments, such as carbon nanotubes (CNTs). For instance, anomalies in diffusion, viscosity, and the spontaneous entry of water into hydrophobic channels are among the phenomena that emerge from the complex interaction between water molecules and carbon walls [2, 3]. However, the microscopic investigation of water confined within CNTs presents several challenges. Traditional simulation methods, such as classical molecular dynamics (MD), rely on empirical potentials derived from experimental data, which often suffer from limited accuracy and transferability. In contrast, first-principles approaches, such as density functional theory (DFT), offer higher precision but are computationally prohibitive for large systems and long timescales. In this context, deep neural network force fields – also known as Deep Potential (DP) – have emerged as a promising strategy to bridge this gap by combining DFT-level accuracy with efficiency close to that of classical MD [4, 5]. Here, we propose the development of a machine learning potential specifically trained to model liquid water and water confined in CNTs. The potential was constructed based on physically motivated sampling, including a minimal set of configurations of liquid water and of water confined in CNTs, where the CNTs have different chiralities and diameters. We present the validation procedure, highlighting the extrapolation capabilities of the DP, as well as the finite-size effects on the dynamical and structural properties of confined water.

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Explorative Relaxation Redistribution Method for Saddle Point Discovery in Molecular Simulations

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The characterization of rare events and transition pathways in molecular systems remains a central challenge in atomistic simulations, with wide-reaching implications across physics, chemistry, and biology [1]. In order to address that challenge, several methods have been proposed in the literature [2-4]. In this work, we specifically discuss the **Explorative Relaxation Redistribution Method (ERRM)** [5], as an extension of the iMapD method [6], designed to automatically locate fixed points, including saddle points, in complex dynamical systems without the need for prior knowledge of collective variables or reaction coordinates.

In particular, ERRM extends the **Relaxation Redistribution Method (RRM)**, which was originally formulated for simplifying stiff dynamical systems describing chemical kinetics [7-8]. The method leverages local manifold learning and dynamic exploration, treating the system as a black-box simulator that may be governed by deterministic or stochastic differential equations. ERRM iteratively constructs local second-order approximations of the slow invariant manifold (SIM) and exploits a dynamic surfing strategy to navigate the phase space. Our implementation offers preliminary demonstration on ERRM's ability to efficiently locate saddle points and reconstruct reaction pathways across a diverse set of benchmark problems. These include the classic Müller-Brown potential, a cylindrical system with metastability governed by stochastic dynamics, and a seven-atom Lennard-Jones cluster where the transition of a central atom to the periphery is captured without bias. In both low- and high-dimensional latent spaces, ERRM exhibits stability and adaptability by adjusting its intrinsic dimension to that of the effective energy landscape's support.

Interestingly, the ERRM can integrate **active learning** techniques to orchestrate exploration in higher-dimensional latent spaces. Additionally, the method constructs a global atlas of local manifold charts, thus offering a fully data-driven parametrization of the explored landscape.

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P13

Probing Aromatic Alkylation Mechanisms in Zeolites via Enhanced Sampling and Machine Learning Potentials

P14

Linking Thermodynamics and Structure in Aqueous LiCl Solutions

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Aqueous electrolyte solutions are central to processes in chemistry, biology, and engineering—ranging from cellular ion transport and protein stability to energy storage and interfacial phenomena such as surface tension modulation. However, their behavior at moderate to high concentrations often deviates from classical models like Pitzer and McMillan-Mayer. Compounding this, historical experimental datasets lacked the precision and concentration range needed for rigorous model validation. In collaboration with Prof. Paul Cremer (Penn State University), we aim to advance both experimental benchmarks and theoretical descriptions of electrolyte solutions. Using high-precision measurements of density and partial molar volumes for LiCl, we have parameterized a classical force field capable of accurately reproducing these properties up to concentrations approaching 9 M. In particular, the model captures partial molar volumes of LiCl derived from density derivatives, revealing strong non-ideal behavior best described by a fourth-order polynomial in concentration. Our simulations show that increasing salt concentration leads to the formation of complex ion-water structures — including 2-, 3-, and 4-body aggregates—which can be understood through microscopic descriptors such as coordination numbers and the topology of evolving ion networks.

Reactive interatomi Potential for mass transport modeling of LIF in Solid Electrolyte Interface

Paolo De Angelis[1,2], **Umberto Raucci**[2], **Francesco Mambretti**[2], **Matteo Fasano**[1], **Pietro Asinari**[1], **Eliodoro Chiavazzo**[1], **and Michele Parrinello**[2]

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The solid-electrolyte interphase (SEI) plays a key role in both the performance and lifetime of lithium-ion batteries (LIBs) [1], yet its atomistic transport properties remain elusive because the highly reactive environment makes challenging the experimental investigation [2]. Also, the modeling techniques, faces several challenges since conventional force fields (FF) fail to capture the intricate chemistry and reactions that emerge at the anode-electrolyte interphase [2].

Our study examines the capabilities of advanced computational modeling techniques to investigate this highly reactive environment, focusing specifically on lithium fluoride (LiF) [3], which is a beneficial inorganic SEI component essential for optimal battery performance.

We compare two types of reactive force fields: the traditional semi-empirical Reactive Force Field (ReaxFF) [4] and the recently developed Machine Learning Force Field (ML-FF), which has garnered significant interest and success [5]. Both FFs are trained using *ab initio* Density Functional Theory (DFT) data.

The enhanced accuracy of these models allows for more precise molecular dynamics (MD) simulations, offering detailed insights into the mechanisms and dynamics of lithium-ion transport *in operando* condition and at an atomistic scale with first-principles accuracy. These simulations create new opportunities to understand how crystal structure and local environments affect ion mobility. Additionally, the flexibility and precision of ML-FFs provide a scalable and reliable approach for investigating more complex, multicomponent SEI strucutre. This ultimately facilitates the *in silico* design of optimized interphases.

In conclusion, our work emphasizes the vital role of innovative force fields in enhancing the modeling of SEIs. Accurate force fields are essential for elucidating and understanding interfacial phenomena in LIBs. They also play a key role in accelerating the optimization of SEIs and the development of next-generation batteries through improved *in silico* experiments and more efficient and accurate material modeling.

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Slow dynamical modes from static averages

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We describe the evolution of a complex system not through long trajectories, but via the study of probability distributions evolution. This more collective approach can be made practical using the transfer operator formalism and its associated dynamics generator. Here, we show that the lowest eigenfunctions and eigenvalues of the dynamics generator can be efficiently computed using data easily obtainable from biased simulations. We also show explicitly that the long time dynamics can be reconstructed by using the spectral decomposition of the dynamics operator [1,2]. Finally, we show the applications of this method to describe the time evolution of biological systems.

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P17

Solvent Fluctuations Shape the Formation of the Hydrated Electron in Photoexcited Water

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The hydrated electron has long captivated scientific interest due to its key role in processes such as DNA damage, redox chemistry, and interfacial reactions[1, 2, 3]. While it is commonly generated using photons above the ionization threshold of water, experiments have shown that it can also form with photon energies as low as 6.5 eV.

In this work, we explore the photogeneration of hydrated electrons by simulating excitation to the first absorption band of liquid water using excited-state molecular dynamics. Our results reveal two competing decay pathways: hydrogen atom transfer (HAT) and proton-coupled electron transfer (PCET). We find that only PCET leads to the formation of a hydrated electron in the excited state. We also show that localization of the electron requires collective translational and rotational motions of surrounding water molecules. Finally, we examine the fluorescence emission of the hydrated electron, as observed experimentally by Tauber et al.[4]. We find that the emission energy is closely linked to both the electron's gyration radius and the distance between the hydroxyl radical and the hydronium ion, providing new insights into the optical signatures of this transient species.

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General Collective Variables from Distributions of Thermodynamic Properties

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Thermodynamically speaking, any physicochemical process coincides with an exchange of enthalpy and entropy. Despite this, when performing computational studies with a finite number of particles, descriptors based on the potential energy are often insufficient due to its inherent noise.

In this work, we adopt the language of distributions to describe states and map distributions of fundamental thermodynamic properties to powerful collective variables, circumventing the need for conventional descriptors that are mere proxies for the process of interest, requiring minimal preexisting knowledge of the investigated system.

The generality of this approach is demonstrated by investigating both a phase transition in a bulk material and a simple protein-ligand system.

Phenol reactivity at the air/water interface

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In the recent years there have been a broad amount of studies suggesting that chemical reactions can be significantly accelerated at water interfaces compared to when they occur in the bulk phase. This phenomena has been coined as "on water" ctalysis by Sharpless and co-workers [1], who have observed that certain organic reactions occur much faster in water suspensions than when conducted in organic solvents.

The molecular origins of this acceleration are a matter of debate in the literature. There are several factors that have been proposed to explain this acceleration like the presence of high electric fields and their flucutations, interfacial solvation and anisotropy of reactants at the interface, the surface activity of hydroxide and hydronium ions and geometrical confinment effects.

In particular, Tahara and coworkers have studied studied the photodissociation of phenol at the air/water interface by the means of ultraviolet-excited time-resolved heterodyne-detected vibrational sum frequency generation (UV-TR-HD-VSFG) spectroscopy [2]. In this way, they have oberved ultrafast dissociation of phenol in a 100 fs timescale, 10^6 orders of magnitud faster than what is observed in the bulk (~5 ns). They argue that this acceleration is due to the lowering of the barrier to go across the conical intersection in the excited state S_1 to the dissociative state.

In this work we studied the system of phenol at the air/water interface by a computational approach. We first conducted Non Adiabatic Molecular Dynamics (NAMD) in order to study the photodissociation at the air/water interface. Based on this simulations we analyzed the mechanism through which the dissociation occurs and we shed some light into the origins of possible acceleration at the interface.

Since the presence of high electric fields at the interface is one of the most invoked origins for surface enhanced reactivity, we then conducted classical molecular dynamics of this system and we analyzed the electric field acting at the midpoint of the OH bond of the phenol at the interface compared to the bulk. We found no significant differences between both systems. At the same time we used the Information Imbalance (II) methodology to evaluate the information content that solvation coordinates have on predicting the electric field on the phenol. In this way we show that most of the information of the electric field can be recovered by solvation features. This then suggest that the treatment of electric field and solvation cannot be considered as two different physical effects.

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Free Energy Decompositions With The Mixture Expansion

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Free energy calculations based on molecular dynamics simulations play a major role in chemical thermodynamics to study a wide range of physical processes such as drug binding, self-assemby, and chemical reactions. The many-body nature of these processes leads to difficulties in handling high-dimensional state spaces and collective effects between the participating chemical species. Therefore, the analysis of free energy calculations in many cases can be simplified through the decomposition of a free energy profile into its fundamental components.

Recent sum frequency generation spectroscopy experimental results demonstrated the importance of synergistic effects in interfacial binding processes of mixed surfactant systems [1]. We were able to justify the experimental findings through a series of free energy calculations, but the exact details of the collective effects underlying the phenomenon of synergistic binding of mixed surfactants weren't fully understood. Therefore, in our followup work, we devised a free energy decomposition scheme called the *mixture expansion* in order to partition the total free energy of the binding process into free energy components due to collective effects between each species, as well as electrostatics and van der Waals interactions [2].

Further exploration of the mixture expansion idea, in combination with consideration of both the cluster expansion theory of interacting gases and Widom's potential distribution theorem led to the development of the more fine-grained decomposition scheme, the *interaction expansion*, which decomposes the total free energy into contributions due to collective effects between the various couplings in the system. The interaction expansion turns out to be the appropriate framework for generalizing the hydrophobic interaction to non-rigid species, and provides a new technique in atomistic simulation, *partially-connected molecular dynamics* [3]. Here we demonstrate the use of the new free energy decomposition scheme, apply it to synergistic binding in mixed surfactant systems and the hydrophobic interaction, and provide an outlook for future development of the technique.

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Quantum Prandtl-Tomlinson

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[1] *Università degli Studi di Milano*
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CNR-IOM, Consiglio Nazionale delle Ricerche—Istituto Officina dei Materiali

The interplay of quantum and thermal effects in low temperature atomic stick-slip sliding is not yet well defined. As a preliminary step preceding any dynamical calculations, we use path integral Monte Carlo[1] and metadynamics[2] to investigate the evolution of static free energy barriers for a spring-dragged point slider on a deformable 1D chain – a generalisation of the standard Prandtl-Tomlinson (PT) model. Specifically, we aim at examining the force – the free energy derivative as a function of dragging coordinate – as it evolves with variable slider-chain coupling magnitude and variable chain stiffness, from classical to quantum upon cooling from high to low temperature. Preliminary results so far obtained in the standard PT model (corresponding to the limit of large stiffness) foreshadow instructive quantum-thermal effects on the effective static barrier.

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HPC Toolkit for Automatic Detection of the Collective Burst Mechanism in Liquid Water

Edward Ntim Gasu [1,2], **Ivan Girotto** [1,2], **Natalia Manko** [1] **and Ali Hassanali** [1]

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[2] *Scuola Internazionale Superiore di Studi Avanzati*

This study aimed to optimize the computational efficiency of an automated algorithm for detecting angular jumps in water molecules [1]. Analysing molecular dynamics data poses performance challenges, especially for big data used to detect high-frequency phenomena. The automated protocol for understanding the collective burst mechanism in liquid water, is an example. We envisaged potential post-processing bottlenecks for text-based input processing using MDAnalysis-XYZ coordinate generators. Compressing custom XYZ trajectories to binary and reconstructing coordinates via NumPy's `frombuffer` function, significantly accelerated input processing. With multiprocessing, Numba-JIT, and Joblib parallelism, we present performance benchmarks, current and future applications of the HPC toolkit for understanding the collective burst mechanism underlying angular jumps in liquid water from considerably large trajectories of neat water, electrolyte solutions, and potential hydrogen-bonded systems.

[1] Offei-Danso et al. (2023). Nat. Commun., 14, 1345.

MDRefine: a Python package for refining Molecular Dynamics trajectories with experimental data

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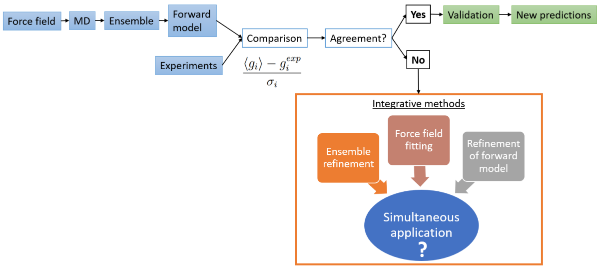
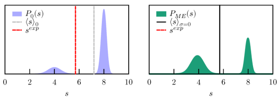
1 – Motivations

MD simulations give access to the conformational dynamics of complex molecular systems, but their capability is limited by the accuracy of force fields. To improve it, several integrative methods can be used, up to now in a disjoint fashion. Here, we introduce *MDRefine*, aimed at implementing the refinement of the ensemble, the force field and the forward models in a combined and customizable way.

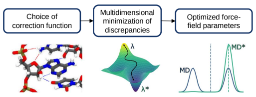


2 – Integrative methods: seamless interpolation of different refinements

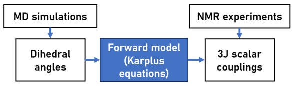
A. Ensemble refinement [3,4,5,6]: optimize the structural ensemble **P** based on max. entropy principle; drawback: the correction on a system is not transferable to different molecules



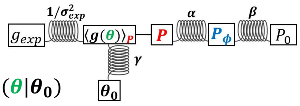
B. Force-field fitting [7,8] is transferable but also sensitive to the choice of correction terms ϕ, with a limited variational freedom in the ensemble



C. Forward-model refinement: to compute the experimental observables from MD simulations, forward models θ are used (e.g., Karplus equations), which have empirical coefficients determined only with a certain accuracy



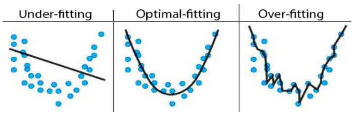
A+B+C: the errors from these different sources mix together, so we suitably combined these integrative methods, taking the best from all of them [8]

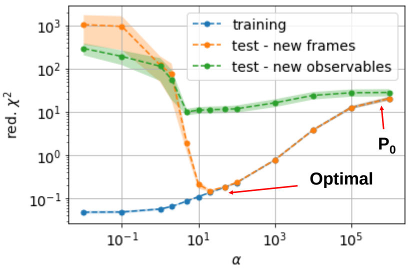


Loss function: $\mathcal{L} = \frac{1}{2}\chi^2[P,\theta] + \alpha D_{KL}[P|P_\phi] + \beta R_1[P_\phi|P_0] + \gamma R_2(\theta|\theta_0)$

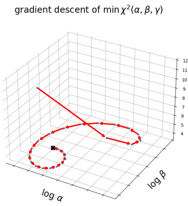
Suitable choice of α, β, γ hyperparameters:

- They regulate the confidence to the initial assumptions (reference ensembles, force field and forward models)
- Their optimal values can be determined in cross-validation through minimization of χ^2 on test set.

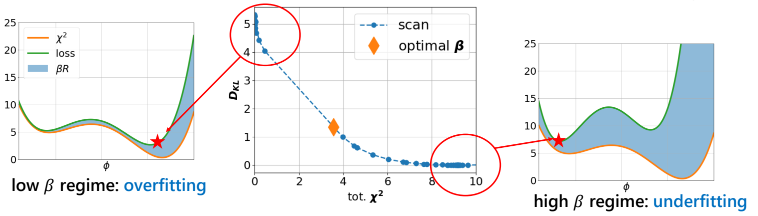




- In high dimension, a scan in the hyperparameter space is cumbersome, so we implemented a direct minimization of ${\chi^2}_{test}$ with (automatic differentiation + implicit function theorem)



- Increasing the hyperparameter $\boldsymbol{\beta}$:

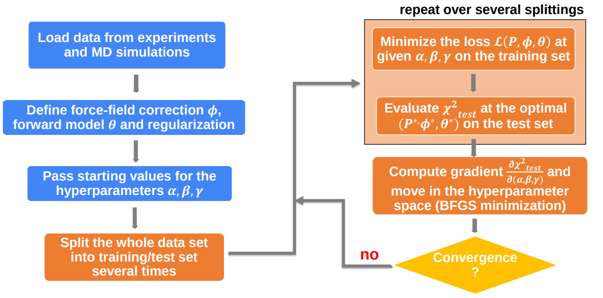


low β regime: overfitting

high β regime: underfitting

3 – Implementing the algorithm

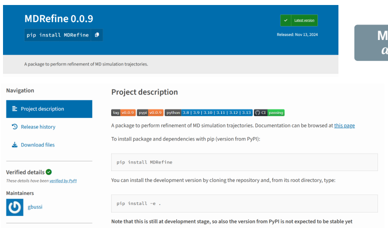
- Python ≥ 3.8
- NumPy, SciPy packages; automatic differentiation with Jax
- Source code, documentation and tutorials available at https://pypi.org/project/MDRefine and https://github.com/bussilab/MDRefine [11]



yes

Minimize $\mathcal{L}(P,\phi,\theta)$ at optimized $\alpha^*,\beta^*,\gamma^*$ on the whole data set

Refinement!



MDRefine 0.0.9

```
pip install MDRefine
```

Released: Nov 13, 2024

A package to perform refinement of MD simulation trajectories.

Verified details

These details have been verified by PyPI

Maintainers

gbussi

Project description

A package to perform refinement of MD simulation trajectories. Documentation can be browsed at this page

To install package and dependencies with pip (version from PyPI):

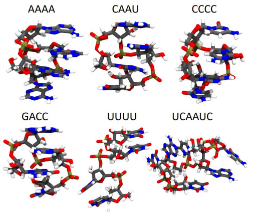
```
pip install MDRefine
```

You can install the development version by cloning the repository and, from its root directory, type:

```
pip install -e .
```

Note that this is still at development stage, so also the version from PyPI is not expected to be stable yet

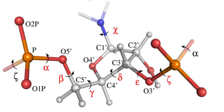
4. A case study: RNA oligomers



MD Simulations [1] with standard OL3 RNA force field and OPC (4-site) water model, 1 μs length, dt = 2 fs, T = 298 K

Experimental observables (from NMR) [2]:

- 3J scalar couplings, for backbone (β,γ) and sugar ν dihedral angles) – simulation values computed through the Karplus equations
- NOE signals, related to distances between H atoms
- unobserved NOE signals – lower boundaries to the signal

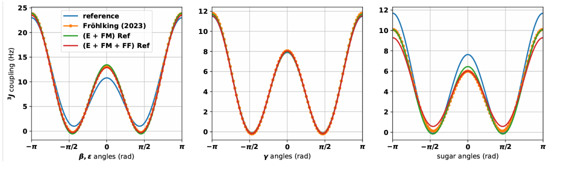


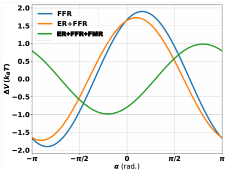
Karplus equations: ($\hat{A} = \beta,\gamma,\nu$ dihedrals)

$${}^3J(\hat{A}) = \theta_1\,(\cos\hat{A})^2 + \theta_2\cos\hat{A} + \theta_3$$

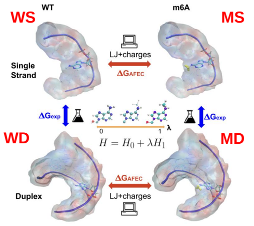
Force-field correction:

$\phi_1\sin\alpha + \phi_2\cos\alpha$





5. Alchemical calculations for methylated adenosine



- Denaturation experiments measure ΔG between single-strand (S) and duplex (D) structures.
- Alchemical calculations estimate ΔG between wild-type (W) and methylated (M) adenosine at fixed structure (S or D).

$\Longrightarrow$ thermodynamic cycle

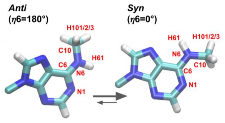
$$\Delta\Delta G_{AFEC} \cong \Delta\Delta G_{exp} \pm \sigma_{exp}$$

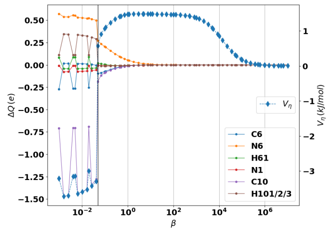
Choice of the regularization: relative entropy [11]

Force-field refinement [10]

Parameters fitted:

- charges of the closest atoms to the methyl group, preserving the total charge
- cosine of η_6 torsional angle N1-C6-N6-C10





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Capturing the Catalytic Choreography of MHETase-Catalyzed Plastic Degradation via a Machine Learning-Based Committor Framework

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Understanding the enzymatic degradation of polyethylene terephthalate (PET) derivatives is essential for improving plastic recycling strategies [1]. In this work, we investigate the hydrolysis of mono-(2-hydroxyethyl) terephthalate (MHET) catalyzed by MHETase [2] using hybrid QM/MM simulations combined with a recently developed enhanced sampling approach based on a machine-learned committor function [3]. This method enables extensive sampling and a statistical characterization of the transition state ensemble, identifying key configurations and weighting them according to their actual contribution to the reaction dynamics.

Our committor-driven simulations reveal a concerted single-step reaction mechanism and allow to capture the coordinated sequence of substrate positioning, nucleophilic attack, and proton relay that underpins MHETase catalysis. A central feature of this mechanism is the dynamic role of His528 in the Asp492-His528-Ser225 catalytic triad. Our simulations show that the protonation state at the Nϵ position of His528 critically modulates the basicity of the Nδ site, enabling it to abstract a proton from Ser225. This proton transfer is essential for generating the Ser225O^{-} nucleophile necessary for attacking the MHET ester bond. Simultaneously, the protonation state of the carboxylate group of the MHET is influenced by nearby Ser416 and Arg411 residues of the enzyme, which fine-tune the local hydrogen-bonding network and electron density across the substrate. This dual modulation acts in concert to orchestrate the hydrolysis mechanism within the MHETase active site, ensuring precise alignment and reactivity for efficient MHET ester bond cleavage.

Our findings highlight the potential of this machine-learning-based enhanced sampling scheme to study rare events in complex biochemical systems, offering a powerful tool for unveiling mechanistic details that are often elusive with traditional simulation approaches, and paving the way for accelerating the rational design of novel enzymes through more accurate dynamics-activity correlations targeting the transition state ensemble.

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Simulating aggregates of (bio)molecules to connect structure and properties

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Molecular aggregates are a challenging case to model from scratch, as often there is little experimental information about the details of their structure. However, such details - involved in the intermolecular interactions, are crucial to determine their properties, and namely the response to light in terms of optical properties, photophysics or photochemistry.

I report here a few cases where atomistic modeling in the form of molecular dynamics (MD) is employed to model a reliable structure for the aggregate. The structural information is often coarse-grained, either for the purpose of driving the structural exploration (enhanced sampling MD), either to parametrise a coarse-grain electronic model useful to simulate (chiro)-optical properties for the interacting assembly.
In the cases of aggregates of chiral organic molecules, we first show how such hybrid modeling scheme can offer a valuable way to decipher experimental results [1,2]. With the objective to interpet and simulate absorption and circular-dichroism spectra of such aggregates, the structural guess produced from MD is employed for an essential state electronic model. In another ongoing research direction, an MD-based robust methodology is established to produce structural guesses of assemblies of biologically relevant molecules, with the objective to assist the interpretation of their photochemistry [3].

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Global Optimization of Large Molecular Systems Using Rigid-Body Chain Stochastic Surface Walking

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The global potential energy surface (PES) search of large molecular systems remains a significant challenge in chemistry due to "the curse of dimensionality". To address this, here we develop a rigid-body chain method in the framework of a stochastic surface walking (SSW) global optimization method, termed rigid-body chain SSW (RC-SSW). Based on the angle-axis representation for a single rigid body, our algorithm realizes the cooperative motion of connected rigid bodies and achieves the coupling between rigid-body chain movement and lattice variation in the generalized coordinate. By exploiting the numerical energy second derivative information on rigid bodies, RC-SSW can optimize the global PES of large molecular systems with an unprecedentedly high efficiency. We show that RC-SSW is more than 10 times faster in locating the model protein global minimum while revealing many more low energy conformations than molecular dynamics and can identify low energy phases of molecular crystals up to 172 atoms missed in the sixth CCDC blind test.

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P27

Thermal Transport in Lithium-ion Batteries using Molecular Dynamics Simulation

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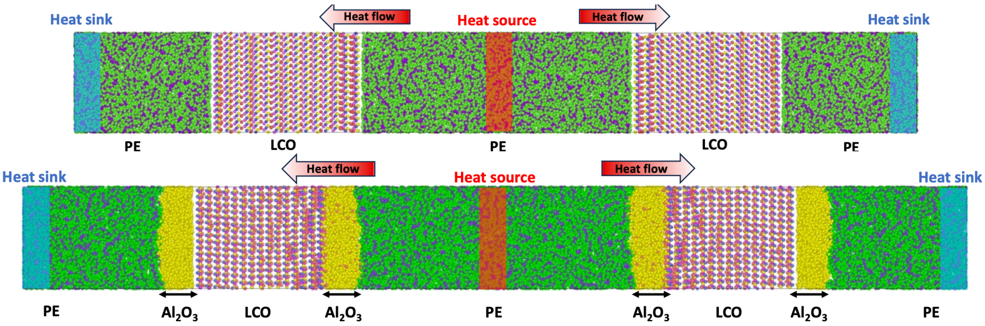
This study investigates the effect of an amorphous aluminum oxide (Al_2O_3) interlayer on the interfacial thermal conductance between the cathode ($LiCoO_2$, LCO) and polyethylene (PE) separator in lithium-ion batteries using non-equilibrium molecular dynamics (NEMD) simulations. Thermal regulation remains a major challenge in high-energy-density batteries, especially at material interfaces where heat dissipation is limited.

PE/LCO bilayer systems, with and without a 1-nm Al_2O_3 interlayer, were modeled using the CVFF force field. A temperature gradient was applied along the z-direction using the Müller-Plathe method, and interfacial thermal conductance was calculated. Results show a significant enhancement from 102.6 MW/m^2K (PE/LCO) to 206.6 MW/m^2K with the Al_2O_3 interlayer.

Vibrational density of states (VDOS) analysis indicates improved phonon coupling due to the spectral overlap between the Al_2O_3 and adjacent layers. Binding energy calculations support strong interfacial adhesion, particularly between Al_2O_3 and LCO. These findings suggest that Al_2O_3 interlayers can substantially improve thermal transport at critical interfaces, enhancing safety and performance in future battery designs.



Schematic of heat flow across PE/LCO and PE/Al_2O_3/LCO interfaces

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WATER BRIDGING SITES IN COLLAGEN MICROFIBRILS: AN OCCUPANCY-BASED ANALYSIS FROM MOLECULAR DYNAMICS

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Water molecules play a vital role in stabilizing the triple helical structure of collagen through transient hydrogen-bonded bridges. While previous studies have examined these interactions in isolated tropocollagen molecules [1], the current study investigates water-mediated bridging in a more physiologically relevant collagen microfibril model, consisting of seven aligned tropocollagen units arranged in a quasi-hexagonal configuration.

Using classical MD simulations in an NPT ensemble for 40 ns we identified water molecules residing longer than 2 ns within the first hydration shell of the fibril and analyzed their interactions with nearby collagen atoms. A combination of RMSD filtering, STFT analysis, and geometric criteria was employed to identify translationally restricted time periods of water molecules and their associated bridging sites.

Using data driven and assumptive method based on previous studies [1] were used to identify water bridges. We observed both intra-triple helix bridges and new multi-atom binding patterns, especially in overlapping regions of the fibril. We were able to identify calculating torsion angles [2] that the helical unwinding is temporally correlated with water ingress into the helical cavity, The N–H–O angles during these events of water molecule entering and exciting the helical cavity were consistently >120°, indicating strong hydrogen bonding.

Directional diffusion coefficients of water within the first hydration shell, along the fibril's Z axis revealed anisotropic mobility of water. which are slower than bulk water and align with prior collagen hydration studies [3]. Our findings reveal that enhanced molecular restriction and water bridging within the fibril arise from both structural confinement and dynamic helical perturbations.

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P29

Causality as a prob to distinguish hidden behaviors in molecular dynamics

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In molecular dynamics, systems with many degrees of freedom pose a fundamental challenge: how can we characterize their behavior in a meaningful way? This question can be approached with various angles, from identifying high-level collective variables that capture essential mechanisms to training dynamic equations that reveal correlations and concerted behavior within the system.

In this work, we use a non-commutative measure called information imbalance to investigate causal relationships between collective variables (CV) selected from molecular dynamics simulations[1]. This tool allows us to track how the causal links between these variables evolve in response to changes in simulation parameters.

To illustrate this, we examine the interaction between the orientation of a single water molecule's dipole moment and the average dipole moment of its first solvation shell. We apply this analysis to NPT simulations conducted under both ambient conditions and near the critical point of the liquid–liquid transition in supercooled TIP4P/2005 water. Our goal is to understand how the causality between these variables changes in a transformation that so far has resisted to many geometric characterizations.[2, 3]

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P30

RNA recognition-driven closing of spliceosome: complex conformational transformations via all atom simulations

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RNA splicing is a crucial stage in gene expression wherein introns are removed from precursor (pre-)RNA and exons are joined to form mature RNA product, either protein-encoding mRNA or functional non-coding RNA. The spliceosome, a complicated ribonuclear machine, is responsible for correct pre-RNA splicing [1]. Spliceosome is composed of five small nuclear RNAs (snRNA) and tens of associated protein factors, which all undergo dynamical conformational changes. One of the important conformational transitions is the formation of the Bact spliceosome associated with a substantial conformational change of the SF3b splicing factor, in which the SF3b complex transitions from an open to a closed conformation upon recognition of a key signaling sequence of pre-RNA (i.e. the so-called the branch point sequence). During this process the pre-RNA is engulfed and the bulged branch point adenosine (BPA), which serves as nucleophile in the first splicing reaction, is positioned in a specific pocket [2]. Cryo-EM studies have made tremendous strides in shedding light into the splicing process [3,4], however they mostly provide static snapshots, while computational techniques can uncover the dynamical transformation between different stages in the splicing cycle and thus help fill-in the gaps between experimental results.

The conformational change that the SF3b complex undergoes is essential for understanding key aspects of splicing, however all atom simulations of this process, even boosted using ‘traditional’ enhanced sampling techniques, are challenging due to the size and complexity of the system and the large conformational rearrangements involved. To overcome this challenge, we applied the deepLDA machine learning approach [5] to obtain a collective variable that can describe such complex conformational transformation. Set of distances and angles between distinct part of the SF3b complex [6] served as the input parameters that were compressed by deepLDA into a single collective variable able to discriminate the Open and Closed states of SF3b complex. Using this collective variable, in combination with well-tempered metadynamics and umbrella sampling, we simulated the opening/closing of the SF3b complex thus obtaining key mechanistic insights into spliceosome function.

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Computing the Committor Function for Enhanced Sampling Simulation

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The problem of studying rare events is central to many areas of computer simulations. In a recent paper[1], we proposed a method of solving this problem passes through the computation of the committor function. We base our method on the variational principle to which it obeys and we find its minimum through a self-consistent procedure that starts from information limited to the initial and final states. And through this method, the transition state ensemble could be efficiently sampled. Most recently, we greatly ameliorated this procedure by combining it with a metadynamics-like enhanced sampling approach in which a logarithmic function of the committor is used as a collective variable[2]. This integrated procedure leads to an accurate and balanced sampling of the free energy surface, extensively sampling the transition state region as well as the metastable basins, thus allowing for accurate free energy calculations upon reweighting. We show that our approach can be used in cases in which competing reactive paths are possible and intermediate metastable are encountered and how physical insights can be obtained from the optimized committor model and the sampled data, thus providing a full characterization of the rare event under study.

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P32

NMR crystallography at finite temperatures

Isatin Derivatives as Antimicrobial Candidates: A Theoretical Approach Using DFT and MD Simulations

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ABSTRACT: Microbial infections remain a significant threat to global healthcare. Among the most common culprits are *Escherichia coli* (E. coli), a Gram-negative bacterium, and *Staphylococcus aureus* (S. aureus), a Gram-positive bacterium [1]. Although antibiotics have long been essential in combating these pathogens, their growing inefficacy due to bacterial resistance and misuse of antimicrobials has driven the search for new therapeutic agents [2]. Isatin derivatives, recognized for their clinical importance, have exhibited antimicrobial properties against *S. aureus* and *E. coli* in both in vivo and in vitro research [3, 4]. This study explores four such compounds (**3a**, **3b**, **3c**, and **3d**) through Density Functional Theory (DFT) and Molecular Dynamics (MD) simulations to assess their interactions with bacterial proteins from *E. coli* and *S. aureus*. The effects of aqueous environments were included to better mimic physiological conditions [5, 6]. Vibrational analysis identified key in-plane and out-of-plane bending associated with CC and CH groups. Frontier Molecular Orbital (FMO) results indicated that compound **3c** exhibited the highest reactivity (Egap = 2.880 eV), followed by **3d**, **3a**, and **3b**. These findings were further supported by Molecular Electrostatic Potential (MEP) surfaces, Noncovalent Interaction (NCI) index, and Natural Bond Orbital (NBO) studies. Docking simulations revealed that compound **3c** had the strongest binding affinity for *S. aureus* (−8.8 kcal/mol), while all four compounds displayed similar interactions with *E. coli*. A 200 ns MD simulation confirmed the stability of these complexes, with **3c** showing the lowest MM-GBSA binding energy against *S. aureus* (−35.6 kcal/mol). Additionally, **3c** and **3d** exhibited favorable binding energies with *E. coli* (−18.6 and −24.3 kcal/mol, respectively). Overall, the combined DFT and MD findings highlight the potent antimicrobial potential of these isatin derivatives, particularly compound **3c**, against both bacterial strains.

KEYWORDS: Isatin derivatives; antimicrobial agents; DFT calculations; molecular docking; MD simulations.

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P34

Semi-empirical Metadynamics Simulations to Unravel Glycosylation Reaction Mechanisms

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Synthetic oligosaccharides are indispensable tools in chemical glycobiology, to unravel and manipulate the role of these important biomolecules in biological processes. However, the synthesis of oligosaccharides is an arduous and labor-intensive process, requiring a significant amount of time-consuming trial-and-error to optimize the glycosylation reaction used to build the target oligosaccharide. Several reaction paths can be followed in the chemical union of two carbohydrate building blocks and these pathways determine the overall stereoselectivity of the glycosidic bond forming process.

In this research, front- and backside glycosylation reactions between a constrained glucose donor and ethanol-derived acceptors with varying nucleophilicities have been investigated in silico. Density functional tight binding-based (GFN-xTB) molecular dynamics simulations have been performed to capture the full complexity of the reaction systems by including dynamical and solvent effects explicitly. Moreover, these simulations are combined with multiple walker well-tempered metadynamics in order to accelerate the crossing of free energy barriers. Contrary to general expectations, we find that the front- and backside reaction paths are both viable for the systems under investigation and show a similar free-energy activation barrier. However, the backside mechanism is more S_N2-like, whereas the frontside mechanism proceeds via an S_N1-like pathway.

P35

Long-Range Electrostatics in Message-Passing Neural Network Interatomic Potentials

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Machine-learning interatomic potentials (MLIPs) bring quantum-level accuracy to large-scale atomistic simulations by learning energy and force maps from first-principles data, yet nearly all state-of-the-art MLIPs rely on a purely short-range description of atomic interactions. While this locality captures many bulk properties, it fails whenever long-range electrostatics—such as in ionic crystals, polar interfaces, or molecular complexes—play a decisive role. Here we introduce a simple, efficient extension that augments any short-range MLIP with learned long-range multipoles. Using the same local environment descriptor, our model predicts per-atom charges and dipoles and feeds them into a classical Ewald or particle-mesh solver. To faithfully restore electrostatics without sacrificing performance, we train these multipoles to reproduce Born effective charges, capturing both ionic displacements and the accompanying electronic polarization. We demonstrate its accuracy on NaCl—reproducing the longitudinal–transverse optical phonon splitting—and on liquid water's infrared spectrum, both in excellent agreement with first-principles benchmarks, at a computational cost comparable to conventional short-range MLIPs.

P36

Predicting Acid–Base Equilibria with Machine-Learned Path Integral Simulations

We present a computational framework for predicting the equilibrium constants of acid–base dissociation reactions involving phosphoric acid and its conjugate bases, combining accuracy, efficiency, and generalizability. Our approach leverages path integral molecular dynamics (PIMD) to incorporate nuclear quantum effects (NQEs), which are crucial for accurately modeling proton transfer. The simulations are powered by a state-of-the-art machine learning interatomic potential, the Point Edge Transformer (PET), and its transferable, “universal” model, PET-MAD. Using this setup, we compute the dissociation constants at the hybrid GGA level of theory and achieve excellent agreement with experimental values. Our results highlight the potential of combining MLIPs with quantum dynamics to study acid–base chemistry with first-principles accuracy. The method is general, computationally affordable, and readily applicable to other systems involving proton transfer, including those relevant to biochemistry and catalysis.

P37

Investigating the Structural Stability and Solvation of Irinotecan in Water and Organic Solvents: A Molecular Simulation Study

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Irinotecan is a synthetic drug that belongs to the topoisomerase I inhibitor class. It treats several cancers, including colorectal, lung, and ovarian. Despite its usefulness, irinotecan has significant drawbacks, including those related to solubility: low bioavailability (or aqueous solubility), toxicity, and limited solubility in a range of solvents as a synthesis, production, and formulation. Although recent studies have sought to improve the drug's pharmacological qualities, little attention has been paid to its solvation behavior. In this work, we investigate how solvents affect the physicochemical properties of irinotecan. We used molecular dynamics simulation to conduct thorough structural studies of the solvation mechanism of irinotecan in water and 10 pure organic solvents, as well as solvation-free energy calculations, to determine the relative solubility. We find that hydrogen bonding between the irinotecan and the solvent dominates the solvation process. Moreover, we observe that the solubility and structural stability of the drug vary depending on the solvent used, with the solubility being higher in cyclohexane than in water.

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P38

Tentative title: "Harnessing Atomic Simulations to Enhance Energy Conversion Technologies"

Aqueous $BiVO_4$ Interfaces via First-Principles and Machine-Learning Simulations: From Electronic Structure to Computational Spectroscopy

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Photoelectrochemical interfaces require accurate modelling of both interfacial energetics and vibrational signatures under realistic, solvation conditions [1]. In our recent study [2], we used first-principles molecular dynamics with the SCAN functional to quantify how water, thermal fluctuations, and oxygen vacancies affect the electronic structure of the $BiVO_4$(010) surfaces. We found that solvation significantly shifts the band alignment with respect to water redox potentials, relative to the dry surface, particularly for Bi-rich and defective surfaces, highlighting the need to account for both temperature and surface composition in the modelling of photoanodes.

Building on these insights, we predict vibrational spectra of $BiVO_4$/water interfaces based on nanosecond-scale machine-learning molecular dynamics. A high-dimensional MACE-based potential [3] is trained on thousands of DFT-SCAN configurations [2], including stoichiometric and Bi-rich surfaces. The model is iteratively refined via active learning to ensure robust performance across complex interfacial environments.

Vibrational spectra are computed using velocity–velocity autocorrelations [4], thus capturing anharmonic and dynamical effects. For stoichiometric $BiVO_4$(010) in contact with water, the predicted spectra reveal minimal surface hydroxylation and a moderately ordered interfacial water structure. In contrast, Bi-rich and hydroxylated terminations exhibit stronger spectral features and altered hydrogen-bonding, consistent with their different surface chemistry. Our results provide vibrational signatures useful to identify interfacial structures in solvated photoanodes.

Our work connects ab initio energetics and machine-learned spectroscopical features and delivers a comprehensive, predictive framework to understanding semiconductor/water interfaces.

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Benchmarking the effect of divalent and monovalent metal ions on RNA structure

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RNA molecules are crucial for a variety of biological functions due to their ability to adopt complex structural folds. Stability and functionality of such complex molecules is closely related to the presence of counterions neutralizing the backbone, both mono- and divalent ions. While the role of the most abundant Mg2+ ion in shaping the RNA molecule is well-established, recent studies show that other ions may also play significant role in RNA catalysis and folding. While dedicated methods towards detection of ions in complex systems are being developed, recent evidence shows that some of the Mg2+ ions may be substituted with K+ ions.

In my project I employed both classical and quantum-classical molecular dynamics (MD) simulations to determine the function of various divalent and monovalent ions in selected RNA systems differing in size and function, whose experimental structures have been reported in the presence of divalent and/or monovalent ions. The challenge in the accuracy of the MD simulations lies in the accuracy of force fields used to parameterize the monovalent and divalent ions and their interactions with the phosphate backbone. Currently, multiple parameterizations for both mono- and divalent ions are available, therefore my plan is to assess the performance of the developed parameters and establish a dependable set of parameters for both monovalent and divalent metal ions that can be effectively and reliably utilized to perform MD simulations of RNA systems and aid in metal ion assignment. While RNA molecules have gain importance in various medical and biochemical applications, the outcome of such a project will become beneficial in biochemistry, biotechnology, and medicine, potentially influencing future research and therapeutic strategies.

Defects at Play: Shaping the Photophysics and Photochemistry of Ice

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Light-induced reactions in ice play a pivotal role in environmental, atmospheric, and astrophysical processes [1-3], yet the microscopic origins of photoproducts from UV interactions remain poorly understood [4,5]. Here, we explore the photochemistry of ice Ih using time-dependent hybrid density functional theory [6,7] on various pristine and defective ice models. Our investigation of the excited state potential energy surface reveals that UV absorption can lead to the formation of hydronium ions, hydroxyl radicals and excess electrons. One of the dominant mechanisms of decay from the excited to the ground-state involves the recombination of the electron with the hydroxyl radical yielding hydronium-hydroxide ion-pairs. We find that this recombination pathway is highly sensitive to lattice defects, including vacancies and pre-existing photoproducts. We also observe that UV excitation leads to the formation of Bjerrum defects and suggest that, together with hydroxide anions, they likely contribute to the spectral features seen after prolonged UV exposure [4,5], which are markedly red-shifted relative to those observed after short exposure [8]. These findings highlight the critical role of defects in shaping the onset of absorption and emission processes in ice.

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Allosteric signalling in CRISPR-Cas9

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Structure-Based Design of 1,3,5-Triazine Derivatives Targeting *Plasmodium falciparum* Heat Shock Protein 70-1 and *Mycobacterium tuberculosis* Dyhydrofolate Reductase (*Mtb*DHFR).

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Malaria, caused by *Plasmodium* parasites, has led to approximately 1.2 billion cases and 2.7 million deaths globally from 2018 to 2022, predominantly due to *Plasmodium falciparum* in the WHO African Region. The emergence of drug-resistant strains underscores the urgent need for new, target-specific anti-malaria drugs [1-3]. This project focused on designing 1,3,5-triazine-2-amine derivatives as inhibitors of P. falciparum heat shock protein 70-1 (PfHsp70-1). A diverse library of 99 derivatives was created using structure-based and fragment-based methods, ensuring synthetic accessibility through click chemistry. A final library of 50 unique compounds, all adhering to Lipinski's rule of five, was generated. The designs process was validated with molecular dynamics and molecular mechanics simulations revealing the protein-ligand stability. Molecular dynamics simulations demonstrated strong protein-ligand stability, with binding free energies reaching -37.96 kcal/mol for the top compounds, promising new therapeutic options for malaria treatment.

In parallel, a research into 1,3,5-triazine-2-amine derivatives as potential anti-tuberculosis compounds, targeting MtbDHFR was also studied. A library of 1,700 compounds was computationally generated focusing on selectivity between human-DHFR and MtbDHFR. Twenty-three compounds showed favorable inhibition of MtbDHFR. Virtual screening and ADMET studies were conducted to evaluate binding affinities and pharmacokinetics. Molecular dynamics simulations confirmed excellent binding affinities, ranging from -6.5 to -14.1 kcal/mol, indicating that 1,3,5-triazine scaffolds hold significant promise for developing effective anti-TB leads, contributing to global health efforts against this disease.

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Data-Driven Discovery of the Origins of UV Absorption in Alpha-3C Protein

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Over the last decade, there has been a growing body of experimental work showing that proteins devoid of aromatic and conjugated groups can absorb light in the near-UV beyond 300 nm and emit visible light. Understanding the origins of this phenomena offers the possibility of designing non-invasive spectroscopic probes for local interactions in biological systems. It was recently found that the synthetic protein α_3C displays UV-vis absorption between 250-800 nm which was shown to arise from charge-transfer excitations between charged amino acids. In this work, we use data-driven approach to re-examine the origins of these features using a combination of molecular dynamics and excited-state simulations. Specifically, an unsupervised learning approach beginning with encoding protein environments with local atomic descriptors, is employed to automatically detect relevant structural motifs. We identify three main motifs corresponding to different hydrogen-bonding patterns that are subsequently used to perform QM/MM simulations including the entire protein and solvent bath with the density-functional tight-binding (DFTB) approach. Hydrogen-bonding structures involving arginine and carboxylate groups appear to be the most prone to near-UV absorption. We show that magnitude of the UV-vis absorption predicted from the simulations is rather sensitive to the size of the QM region employed as well as to the inclusion of explicit solvation.

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From Molecules to Biomolecules: A Data-Driven Many-Body Perspective on Aqueous Systems Across All Phases

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Achieving chemical accuracy in molecular simulations of aqueous systems has remained a central challenge for decades due to the interplay of many-body interactions and nuclear quantum effects. In this contribution, I will introduce a unified, data-driven many-body (MB) formalism that has enabled realistic simulations of water and aqueous systems from small gas-phase clusters to bulk solutions and interfaces. Our data-driven many-body potential energy functions, such as MB-pol and its extensions, systematically integrate physics-based representations with machine-learned components trained on coupled-cluster reference data. This approach not only reproduces structural, thermodynamic, and spectroscopic properties of aqueous systems across all phases, but also accurately predicts emergent phenomena such as the location of the liquid–liquid critical point in supercooled water. I will also show how the MB formalism bridges the gap between density functional theory (DFT) and chemical accuracy by enabling the development of density-corrected functionals. In particular, I will highlight our recent simulations of water autoionization, which yield a quantitative estimate of the autoionization constant and reveal the importance of nuclear quantum effects in stabilizing solvent-separated ion pairs via the Grotthuss mechanism. Finally, I will show how our MB formalism is being extended to simulate biomolecules in aqueous environments with coupled-cluster accuracy, thus paving the way for predictive simulations of biological systems under realistic conditions.

Supramolecular cooperativity through the lens of enhanced sampled molecular dynamics.

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Supramolecular polymers are dynamic aggregates whose properties arise from reversible, non-covalent interactions. A central aspect in the design and function of these materials is the *cooperativity* of polymerization—by which the addition of monomers becomes increasingly favorable as the polymer grows.[1] Cooperativity strongly influences both the structure and collective behavior of the resulting supramolecular materials, with significant implications for their mechanical, optical, and self-healing properties. Understanding the origins and consequences of cooperative effects is therefore crucial for the rational design of new functional Supramolecular polymers.

In this work, we systematically explore the cooperativity of supramolecular polymer systems via Molecular Dynamics simulations, powered by On-the-fly Probability Enhanced Sampling (OPES)[2] to accurately characterize the free-energy landscape associated to the key polymerization steps. We first prove our approach by studying the polymerization of ad-hoc, simplified CG models of cooperative and non-cooperative self-assembling monomers.[3] We then extend our analysis to a chemically realistic supramolecular polymer system based on ureidopyrimidinone (UPy) motifs. Upy is a widely used molecule in biohydrogel design [4], for its potential in creating polymer networks that reproduce the properties of extracellular matrix polymers. Our simulations provide clear insights into the microscopic origins of Upy cooperativity thereby underscoring the importance of the proposed molecular simulation approach in guiding the development of next-generation supramolecular materials.

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Data-efficient Modeling of Catalytic Reactions via Enhanced Sampling and On-the-fly Learning of Machine Learning Potentials

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Simulating catalytic reactions under operando conditions remains a central challenge in computational catalysis, primarily due to the complex and dynamic nature of active sites and the prohibitive cost of quantum mechanical (QM) simulations over realistic timescales. While machine learning (ML) potentials can replicate QM accuracy at a fraction of the cost [2], their construction requires representative training data that capture rare events and transition states, which are inherently difficult to sample efficiently.

Here, we present a data-efficient and modular framework that integrates enhanced sampling and active learning to develop accurate ML potentials for catalytic systems [1]. In the exploratory phase, we perform uncertainty-aware molecular dynamics using Gaussian Processes (GPs) and On-the-Fly Probability Enhanced Sampling (OPES) to drive the system along relevant reaction pathways and identify critical configurations. This is followed by a convergence phase in which a graph neural network (GNN) potential is trained and refined using a novel Data-Efficient Active Learning (DEAL) strategy. DEAL combines query-by-committee uncertainty from the GNN with GP-based local environment descriptors to systematically select configurations for QM refinement.

We apply this approach to ammonia decomposition on FeCo alloy surfaces, a bimetallic catalyst known for higher activity than pure Fe [3], yet still lacking a detailed microscopic understanding due to the high computational cost of DFT simulations. Our methodology reveals complex, multi-channel reaction mechanisms, including $NH_3 \rightarrow NH_2 + H$, $NH_2 \rightarrow NH + H$, and $NH \rightarrow N + H$ steps. Free energy profiles, reconstructed with a sampling error below 20 meV, uncover ensembles of transition states and parallel reaction pathways featuring similar barriers but distinct geometries. The ML potential accurately captures catalytic behavior under realistic conditions, including lateral interactions, and reveals the microscopic origin of the enhanced activity of FeCo alloys compared to pure Fe, which we attribute to both a reduction in the activation barrier of the rate-limiting step and increased resistance to surface nitridation. This study establishes a robust, data-efficient approach for simulating catalytic processes under realistic conditions.

Compared to prior works on similar systems [4, 5, 6, 7], our protocol reduces the number of required DFT calculations by over a factor of 20. The method is thus well suited for the investigation of complex systems and the use of high-level theories, offering a scalable and interpretable path toward realistic modeling of catalytic materials and reaction mechanisms.

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Modelling conformational dynamics in pre-mRNA splicing: How intrinsic flexibility drives RNA strand exchange

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Methanol Desorption from ZnO Surfaces: Key Factors and Catalytic Insights

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The catalytic hydrogenation of CO_2 to methanol is a pivotal reaction in emerging carbon-capture-and-utilisation schemes,[1] yet its overall rate can be limited by how efficiently methanol can disengage from the oxide support. Although ZnO is the industrially preferred promoter for Cu-based catalysts, the atomistic factors that control methanol binding, surface diffusion, and final desorption on different ZnO facets—and in the presence of water or oxygen vacancies—remain poorly quantified in-operando conditions. A predictive picture is hampered by the wide disparity of relevant timescales, ranging from sub-picosecond bond vibrations to second-long rare events. Here we combine ab-initio molecular dynamics with active-learning neural-network potentials and enhanced-sampling simulations to quantify dissociation, diffusion, and desorption of CH_3OH on the four most stable ZnO facets—(100), (110), (111), and (00$\bar{1}$).[2]

The (00$\bar{1}$) surface proves the least retentive: methanol adsorbs weakly and departs rapidly. Both (110) and (100) facets stabilise adsorbed methanol through a cooperative Zn–O–H hydrogen-bond network, leading to slower release and hindered surface diffusion. The (111) facet behaves differently again, undergoing spontaneous reconstruction that favours methanol dissociation into methoxy and hydrogen, effectively locking the fragment to the surface and suppressing molecular desorption. From these models we then inquired the dissociation/recombination of the methanol to/from methoxy, the diffusion on each surface of the molecules, (see Figure 1) and the effect provided by the presence of water molecules on each surface-type.

These facet-resolved free-energy landscapes and rate constants provide a microscopic rationale for the activity on ZnO-based catalysts and offer quantitative targets for tailoring ZnO morphology, defect density, and reaction environment to optimize methanol synthesis.

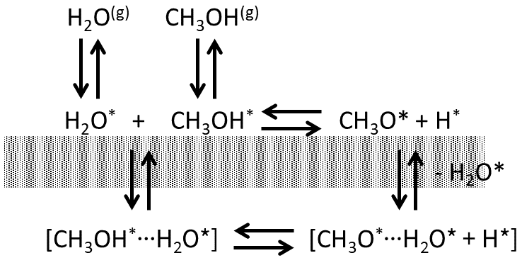

Figure 1: Scheme of the reactions on ZnO-surfaces investigated in this work.

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Conformational Transitions in the DNA Polymerase β: Role of the DNA template sequence and Lys289 residue

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DNA polymerase β (Pol β) plays a central role in the base excision repair (BER) pathway, maintaining genomic stability by filling in small DNA gaps left after damage removal [1]. Mutations in Pol β, such as the K289M substitution, have been linked to various cancers due to their impact on enzyme fidelity and function [2]. Notably, the K289M variant exhibits a significantly increased frequency of incorrect deoxynucleotide incorporation, particularly within a mutation hotspot found multiple times in the adenomatous polyposis coli (APC) gene. A key step in Pol β's mechanism is the conformational transition from an open to a closed state upon nucleotide binding, which is critical for proper substrate alignment during catalysis. In this study, we combine all-atom targeted molecular dynamics (TMD) and transition path sampling (TPS) simulations with our BOLAS free energy algorithm [3,4] to investigate the conformational transition in both wild-type and K289M Pol β, in the presence of a control DNA sequence and an APC-derived sequence associated with colorectal cancer. Our results shed light on how subtle alterations in side-chain conformations caused by the K289M mutation can alter the open-to-closed transition, particularly in the context of the APC sequence. These subtle shifts have profound implications for enzymatic fidelity and may underlie the mutagenic activity of this variant in cancer development.

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Determining the Complete Thermodynamics of Calcite Kink Sites for Crystal Growth and Dissolution

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The competition between growth and dissolution is of key interest in determining the evolution of a crystal system. In the case of many materials where slow growth is observed, the kink sites play an important role in determining where any loss or gain of mass to the crystal will occur. Despite this, it is rare that the thermodynamic stability of individual kink sites is known for a solid growing from solution, except that the average value for a stoichiometric amount is constrained by the solubility of the material. Here we consider the case of the growth of calcium carbonate ($CaCO_3$), which is a highly abundant biomineral fulfilling many roles in nature, including the sequestration of carbon from the environment. In particular, the focus will be on the most stable polymorph at ambient conditions, calcite, which often exhibits predominantly the ($10\bar{1}4$) surface. The interface of this surface with water has been extensively studied using atomic force microscopy [1,2] and X-ray reflectivity [3,4], both of which indicate the presence of ordered water layers.

In this study the focus will be on extending a recently proposed method for determining standard free energies of ion binding at solid-liquid interfaces [5] to predict the 16 distinct kink site free energies at the acute and obtuse steps of calcite. Here the standard free energies for dissolution will be presented based on using both alchemical methods, in which an ion is transferred from the kink site to a 1 M aqueous solution, and via methods in which the ion is removed by following an explicit pathway as a function of distance from the kink site. Both sets of free energies obtained from the two different approaches are found to be consistent with the expected bulk dissolution free energy of calcite, while being radically different from each other. The origin of this difference can be traced to the existence of a substantial interfacial potential at the calcite-water interface due to the ordering of water dipoles. The significance of these results for the growth and dissolution of calcite from aqueous solution will be discussed.

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Interfacial thermal transport at solid/liquid interfaces using machine learning interatomic potentials

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Inverse Design of Molecules with Reinforcement Learning: using Artificial Intelligence in Chemistry without Databases

Enhanced Sampling of Lipid Membrane Fusion via Machine Learning Collective Variables

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Membrane fusion represents a fundamental biological mechanism essential for cellular function and communication, with relevance extending from natural intra- and inter-cellular processes to engineered drug delivery systems. The fusion pathway proceeds through multiple metastable states, with the first being the stalk, a structure consisting of a stable hydrophobic connection between opposing leaflets. While biological fusion is mediated by specialized proteins, synthetic fusogenic agents such as functionalized gold nanoparticles (AuNPs) have been shown experimentally[1] to lower fusion barriers, also offering a simplified and controllable model. Despite several experimental insights, the underlying mechanisms of membrane fusion remain unclear, prompting molecular dynamics investigation.

Previous work in our group[2] focused on system characterization and assessing stalk stability, performing biased simulations using an adaptation of the *chain* collective variable (CV)[3]. Such a CV effectively describes the stalk formation process by counting the fraction of hydrophobic lipid tails within a cylindrical region above the NP. Still, unfortunately, it comes at a significant computational cost. In addition, for technical convenience, these studies relied solely on umbrella sampling simulations, thus providing only limited dynamic insight.

Leveraging the recent implementation of the chain coordinate in PLUMED[4], we adapted the CV to the NP system and tested its performance with other enhanced sampling schemes, including metadynamics[5] and On-the-fly Probability Enhanced Sampling (OPES) variants[6], obtaining results consistent with previous studies. To further improve our computational setup, both in terms of computational efficiency and transferability to other systems, we then explored other CVs based on machine learning approaches. In such a framework, the CV is expressed as the output of a neural network that takes a set of physical descriptors as input. In our case, inspired by the chain coordinate, we selected coordination numbers as input features, to capture the local density of the critical components to fusion dynamics, i.e., lipid tails, water molecules, and ligands. For the optimization of our CV models, we used a classifier-based approach (Deep Targeted Discriminant Analysis, DeepTDA[7]), which only requires information limited to the metastable states and labeled accordingly, as well as a multitask training framework, in order to also incorporate reactive simulation data to improve the quality of the CV in the transition region.

The results obtained with these new setups yielded comparable results with previous work, demonstrating the viability of MLCVs for the study of this kind of systems and significantly improving the computational efficiency. We believe this work establishes a foundation for the computational investigation of more complex membrane fusion processes in the near future.

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An unusual His/Asp acid/base dyad in glycosidase catalysis. Insight from QM/MM MD simulations.

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Glycoside hydrolases (GH) or glycosidases are enzymes that catalyse the hydrolysis of glycosidic linkages in carbohydrates. With almost two hundred families, GHs exhibit diverse functions across a plethora of organisms in nature, being of utmost importance in life. A particular GH from family 117 [1] hydrolyses the α-1,3-glycosidic bonds in agarose, a polysaccharide composed by alternating units of D-galactose and a 4-O-α-3,6-anhydro-L-galactose [2] that is present in the cell wall of marine algae. The bridged structures of anhydro-L-galactose residues in agarose allow for the formation of organized helical structures, resulting in the creation of a high-strength polymer gels which are resistant to degradation, and useful for biotechnological applications. Structural studies suggest that the enzyme uses an unusual catalytic machinery, involving a histidine (His302) as general acid [3], rather than a more conventional carboxylic acid-based residue as in most glycosidases. By means of QM/MM metadynamics, using density functional theory, we investigate the reaction mechanism of Phocaeicola plebeius GH117. We confirm the roles of His302 and Asp90 as the catalytic acid and base residues and show that the positively charged catalytic His shares a proton with a neighbouring aspartate residue, Asp320, which works in tandem with it. Furthermore, we propose a mechanism via a ${}^{1,4}B \rightarrow [{}^{4}E]^{\ddagger} \rightarrow {}^{1,4}B$ conformational catalytic itinerary (B and E refer to Boat and Envelope-like shaped sugar rings) during hydrolysis [4]. We suggest that this mechanism can be extended to other GH families that display a similar His/Asp dyad in the active site, such as GH156 sialidases. These results will be useful in the engineering of enzymes for more efficient processing of marine seaweed.

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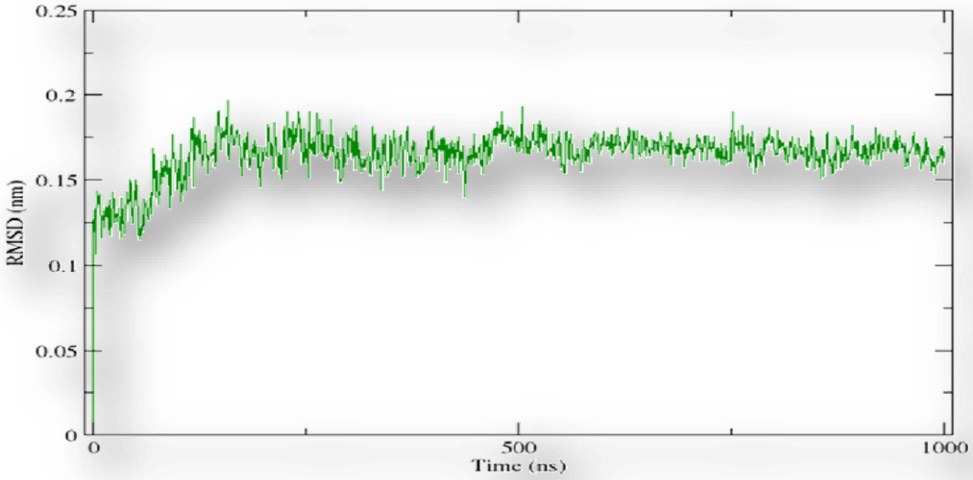
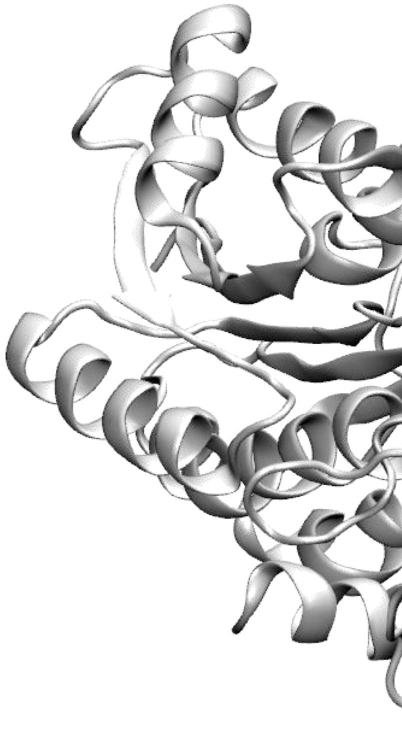
Applying Modeller [1] , to create a model for Sy-LPOR using plant-LPOR as the template and running 1 µs **MD simulation** with Gromacs package [2] .





*Imposing a
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All You Need Is Water: Converging Ligand Binding Simulations with Hydration Collective Variables

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All-atom molecular dynamics (MD) simulations offer detailed insight into chemical and biological processes like ligand binding, but their success is limited by the computationally accessible timescales. Collective variable-based enhanced sampling MD simulations, such as Metadynamics or On-the-fly Probability Enhanced Sampling (OPES), alleviate this problem by introducing a bias potential to accelerate rare events [1, 2, 3]. Selecting effective collective variables (CVs) that capture all relevant system-specific slow degrees of freedom of the system is paramount for the sucess of enhanced sampling simulations but remains challenging. Despite the progress made with data-driven and intuition-based approaches, simple geometric descriptors that are straightforward to implement in any system are still widely used, although they overlook critical slow modes. In particular, in biomolecular events in solution, slowly diffusing water molecules can be a considerable bottleneck [4]. Thus, hydration CVs are promising candidates for more efficient CVs but remain largely underexplored due to the complexity of water behavior. Here, we present a data-driven and automatable strategy to implement robust hydration CVs. We take inspiration from a solvent structure-based tool that quantifies as a fingerprint value the deviations from the uniform radial distribution function of water oxygen atoms. Remarkably, using only these hydration CVs within OPES simulations, we successfully converge the binding free energy landscapes for a series of host-guest systems. These landscapes show excellent agreement with those from more computationally expensive benchmark methods using OneOPES [5, 6]. We further demonstrate efficient convergence relies both on the use of hydration CVs and on the choice of where water is biased, providing clear guidelines for implementation. This work not only underscores the central role of water in molecular recognition but also offers a powerful and generalizable framework for enhancing the sampling of complex biomolecular events.

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Collective effects in liquid water

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Collective effects in solids and liquids are an interesting topic of research that yields information about the structure and dynamics in materials [1]. The collective vibrational excitations in liquids are the corresponding counterpart to phonons in solids. They lead to effects such as the ”fast sound” [2], where the velocity of the propagation speed of mesoscopic acoustic modes is clearly larger than expected from the macroscopic, hydrodynamic value of the adiabatic speed of sound.

Recently we investigated [3] the collective excitations in liquid water using density function theory-based molecular dynamics, and in particular the significance of the inclusion of the London dispersion forces in the description of the interaction between the molecules. We could derive the dispersion of the collective excitations and how the results qualitatively changed when the London dispersion forces were included in the interaction. Other models to describe the interactions in water have also been used to study the collective dynamics in water [4], such as the BK3 model.

Now we extend our former studies on the collective dynamics in liquid water by using recent models of interaction potentials, such as the `MB-pol` [5] and machine learning interaction potentials (MLIPs), such as a foundation model `MACE-OFF23` [6] and an explicitly fitted MLIP [7]. These allow us to perform longer simulations, with larger systems, thus allowing us attain better statistics and smaller wave vectors in the dispersion.

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Nickel-(oxy)hydroxide has emerged as a low-cost electrocatalyst for the OER, contributing to the development of sustainable energy solutions. We address a critical gap in understanding the kinetically sluggish OER on Ni-based catalysts, focusing on the role of structural complexity and charge accumulation on NiOOH surfaces, supported by recent experimental and theoretical evidence linking charge buildup to enhanced catalytic activity. We combine ab initio calculations with state-of-the-art ML potentials to investigate catalyst structures in the presence of water. A systematic exploration of surface configurations and water content—from vacuum to explicit liquid water—via Wulff construction reveals surface thermodynamics at equilibrium and the stabilizing role of water on under-coordinated, potentially active metal sites.

From equilibrium, we examine charge accumulation under applied potential and derive the thermodynamics of surface oxidation sites. Finally, we explore competing OER mechanisms across surfaces, comparing results with electrochemical and XAS data.

Phase Behavior and Structural Ordering of Water under Superhydrophilic Confinement: A Molecular Dynamics Study using the mW Model

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We investigate how superhydrophilic confinement influences the thermodynamic and structural properties of water using molecular dynamics simulations with the coarse-grained monatomic water (mW) model [1,2]. This work builds on our recent study of water confined within slit pores of varying widths and wall-fluid interaction strengths, focusing on properties such as density, enthalpy, potential energy, entropy, specific heat capacity, and structural ordering [1]. Strong wall-fluid interactions significantly alter phase behavior. In narrow pores ($H \leq 20$ Å), the solid phase exhibits higher density than the liquid—an inversion of bulk water behavior—driven by confinement-induced structural ordering. Pronounced hysteresis loops are observed in thermodynamic quantities near transition temperatures, with their magnitude modulated by both pore size and wall interaction strength. Specific heat capacity displays enhanced oscillations due to non-uniform enthalpy changes across temperature intervals, and phase transitions are marked by abrupt shifts in both heat capacity and entropy. Structural ordering is characterized through in-plane orientational and tetrahedral order parameters, revealing the formation of ordered crystalline phases during quenching. These include cubic diamond, hexagonal diamond, and 2D hexagonal structures, whose prevalence varies with confinement conditions. Crystallization is most prominent under stronger surface attraction and narrower confinement, highlighting the role of nanoscale geometry in modulating water's structural organization. These findings provide molecular-level insights into the behavior of confined water, with relevance to nanofluidic systems, biological interfaces, and porous materials. The use of the mW model enables efficient sampling of phase transitions while retaining essential physical characteristics of water. Our results also motivate future investigations that may incorporate multiscale modelling approaches to further explore confinement effects and phase behavior in complex environments.

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`mlcolvar`: the home of machine-learning collective variables

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Most natural processes, due to the large free energy barriers that separate the metastable states, are rare events for molecular dynamics (MD) simulations, making their study challenging. To alleviate this issue and to favour reactive events and better sampling of the phase space, a number of enhanced sampling (ES) methods have been developed, for instance, Metadynamics or On-the-fly Probability Enhanced Sampling (OPES)[1], aim at removing the effect of barriers to promote transitions between states by *filling* the energetic basins. However, such methods typically require the definition of collective variables (CVs) that encode the relevant mode of the process, which are not always easy to determine.

In recent years, machine learning methods have been used to make the design of such CVs simpler and more automatic, directly starting from simulation data. However, despite the increasing number of methods, the lack of a common framework for their development and deployment to common MD and ES engines has somewhat hindered their application and slowed further development. To fill this void, a couple of years ago, we developed `mlcolvar`[1, 2], a general and modular Python library for machine learning collective variables (MLCVs), aimed at making such tools accessible to the whole community of enhanced sampling. The library is indeed structured in a straightforward and modular manner, thus allowing, on the user's side, for a simple employment, and great flexibility on the developer's side, also thanks to a native and efficient interface with the PLUMED[3] plugin for enhanced sampling.

Since its creation, this project has progressively evolved into a small ecosystem covering several aspects not only of CV design and training, but also related to their interpretability and analysis to retrieve physical information from our models. This progress has been fueled by a number of new features. Of course, new CV methods have been proposed and implemented, such as those leveraging the committor function and its properties[4], or those based on learning an approximation of the infinitesimal generator operator that governs the time evolution of simulated systems[5]. In addition, we implemented into the library support for graph neural networks (GNNs), which have recently gained popularity also in the field of MLCVs[6]. Thanks to tools aimed at simplifying the handling of graph data and an additional interface for building the input graphs directly and efficiently in PLUMED, this greatly simplifies the use of GNNs with existing methods and further developments.

Alongside these core improvements, several features have been added to allow for efficient analysis of the obtained CV models and the gathered data. For example, we implemented sensitivity analysis and feature relevance tools for both standard and GNN-based models, functions for post-processing of trajectories, for example, to recover free energy estimates, as well as a simple framework to test and define complex physical descriptors directly from the atomic positions in Python. Last but not least, we made these resources accessible and practically usable also for newcomers or non-coding experts by including, besides standard documentation, a number of hands-on tutorials.

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Potential Functional Changes in Proteins Induced by Carbon Nanotubes: A Molecular Dynamics Study

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A carbon nanotube (CNT) can affect biological systems, ranging from toxicity to changes in functionality. Here, a series of long-scale (1-2 μs) molecular dynamics simulations were conducted to investigate the adsorption and interaction of lysozyme with the CNT, a possible mechanism for altering protein flexibility and function. Four systems were examined: native lysozyme/CNT, denatured lysozyme/CNT, and both systems post-docking. Our results indicate that native lysozyme does not undergo conformational changes when initially captured by a CNT. However, after docking, the native lysozyme/CNT complex exhibits conformational changes. In contrast, the denatured lysozyme binds more effectively to the CNT in pre- and post-docking scenarios. Key amino acid residues, arginine and tryptophan, have been identified as crucial for lysozyme/CNT interactions. The surface of the CNT adsorbs lysozyme through π-π stacking and van der Waals interactions, with these multimodal interactions serving as the main driving force for protein anchoring to the nanotube. These results also underscore the significance of docking in the simulation of protein/nanoparticle interactions. This can lead to entirely different conclusions regarding, for example, the toxicity or functionality of a given nanoparticle life.

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Probing Excited-State Dynamics and Conical Intersection Accessibility via Pump-Probe X-Ray Absorption Spectroscopy in Non-Aromatic Biomolecules

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We present pump-probe UV/X-ray absorption spectroscopy simulations to investigate the excited-state relaxation dynamics of L-glutamine (L-glu) and L-pyroglutamine-ammonium (L-pyro-amm). Non-adiabatic molecular dynamics (NAMD) under the time-dependent density functional theory (TDDFT) framework were performed, employing a hybrid quantum mechanics/molecular mechanics (QM/MM) scheme for L-pyro-amm to account for its crystalline environment, while L-glu was modeled in vacuum. These simulations tracked state population evolution over 500 femtoseconds, and linear-response TDDFT (LR-TDDFT) was used to compute time-resolved X-ray absorption spectra, generating full pump-probe UV/X-ray spectra.

Our objective was to correlate spectral features with conical intersection (CoIn) accessibility, a critical determinant of non-radiative decay. As established previously [1,2], CoIn access in these systems is governed by proton transfer along short hydrogen bonds (SHBs) and carbonyl (C=O) elongation. For L-pyro-amm, SHBs stabilize the excited state by restricting C=O elongation, while L-glu exhibits transient SHB formation that may accelerate CoIn access. Key coordinates, for example proton transfer and C=O elongation, manifest as spectral modulations in X-ray absorption, revealing real-time dynamics of CoIn approach.

These ongoing work may underscore the role of SHB networks in modulating fluorescence through excited-state trapping, consistent with the carbonyl-lock mechanism [1], and highlight X-ray spectroscopy as a tool for probing ultrafast photochemical pathways in biological matter.

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Self-Consistent Hartree+U Modeling of Magnetic Order in Twisted Bilayer and Trilayer Graphene

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Recent discoveries of correlated insulating states, magnetism, and superconductivity in moir graphene multilayer, particularly twisted bilayer (tBLG) and trilayer graphene (tTLG) – have highlighted the need for efficient models that can incorporate both long- and short-ranged electronic interactions. In this work, we present a self-consistent continuum model that incorporates Hartree (long-range Coulomb) and Hubbard (short-range) interactions to study magnetic ordering in these systems. Using magnetic instabilities identified by atomistic RPA calculations, we predict and analyze competing magnetic phases, including ferromagnetic (FM) and antiferromagnetic (AFM) orders in tBLG near the magic angle. Our model successfully reproduces key features of the magnetic phase diagram as a function of twist angle and doping. Furthermore, we extend the method to tTLG and identify stable FM and AFM orders with layer-resolved spin polarization. The self-consistent quasiparticle band structures reveal interaction-induced gap openings and spin splittings, offering insights into the interplay between long- and short-ranged interactions. Our approach provides a computationally efficient and generalizable framework for exploring magnetic ground states in a variety of moir materials.

[1] C. T. S. Cheung, V. Vitale, et al. In preparation

Universal moiré buckling of freestanding 2D bilayers

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The physics of membranes, a classic subject, acquires new momentum from two-dimensional (2D) materials multilayers. Our recent works report the surprising results emerged during a theoretical study of equilibrium geometry of bilayers as freestanding membranes. While ordinary membranes are prone to buckle around compressive impurities, we predict that all 2D material freestanding bilayers universally undergo, even if impurity-free, a spontaneous out-of-plane buckling. The moiré network nodes here play the role of internal impurities, the dislocations that join them giving rise to a stress pattern, purely shear in homo-bilayers and mixed compressive/shear in hetero-bilayers. That intrinsic stress is, theory and simulations show, generally capable to cause all freestanding 2D bilayers to undergo distortive bucklings with large amplitudes and a rich predicted phase transition scenario. Realistic simulations predict quantitative parameters expected for these phenomena as expected in hetero-bilayers such as graphene/hBN, WS_2/WSe_2 hetero-bilayers, and for twisted homo-bilayers such as graphene, hBN, MoS_2 [1]. Buckling then entails a variety of predicted consequences. Mechanically, a critical drop of bending stiffness is expected at all buckling transitions. Thermally, the average buckling corrugation decreases with temperature, with buckling-unbuckling phase transitions expected in some cases, and the buckled state often persisting even above room temperature [2]. Buckling will be suppressed by deposition on hard attractive substrates, and survives in reduced form on soft ones. Frictional, electronic, and other associated phenomena are also highlighted. The universality and richness of these predicted phenomena strongly encourages an experimental search, which is possible but still missing.

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Fine-tuned Global Neural Network Potentials for Global Potential Energy Surface Exploration at High Accuracy

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Machine learning potential (MLP), by learning global potential energy surfaces (PES), has demonstrated its great value in finding unknown structures and reactions via global PES exploration. Due to the diversity and complexity of the global PES dataset, an outstanding challenge emerges in achieving PES high accuracy (e.g., error < 1 meV/atom), which is essential to determine the thermodynamics and kinetics properties. Here, we develop a lightweight fine-tuning MLP architecture, namely AtomFT, that can explore PES globally and simultaneously describe the PES of a target system accurately. The AtomFT potential takes the pre-trained many-body function corrected global neural network (MBNN) potential as the basis potential, exploits and iteratively updates the atomic features (AFs) from the pre-trained MBNN model, and finally generates the fine-tuning energy contribution. By implementing the AtomFT architecture on the commonly available CPU platform, we show the high efficiency of AtomFT potential in both training and inference; and demonstrate the high performance in challenging PES problems, including the oxides with low defect content, molecular reactions, and molecular crystals — in all systems the AtomFT potentials enhance significantly the PES prediction accuracy to 1 meV/atom.

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Correlation between molecular reorientation and dynamical hydrogen bond network in liquid water

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As one of the most fundamental substances, water has been discovered over 70 anomalous properties, e.g., a density maximum at 4 °C under ambient conditions, the increase of compressibility and specific heat when the temperature is decreased. Fundamentally, these anomalous properties primarily originate from the intricate and labile hydrogen bond (H-bond) network whose structure undergoes continuous and dynamic changes, making it challenging to understand. Molecular reorientation represents a highly significant aspect in the evolution of H-bond network, changing the orientation of H-bond. Laage et al. proposed an extended jump model to elucidate the mechanism of molecular reorientation in liquid water and discovered that this process involves sudden large-amplitude angular jumps instead of the commonly accepted sequence of small diffusive steps[1-2]. However, the model struggles to clarify the correlation between reorientation and the evolution of the H-bond network. In our study, leveraging deep potential molecular dynamics[6], we thoroughly examine local topological structures and its dynamical properties[3-5] to unveil the microscopic mechanism underlying molecular reorientation in liquid water.

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Extracting slow modes of protein folding processes and application to enhanced sampling

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Protein folding dynamics can be decomposed into a hierarchy of modes characterized by distinct relaxation times. We apply a recently developed method to extract slow collective modes from equilibrium statistics of the Trp-cage miniprotein. [1] The model reveals that folding and unfolding dynamics are predominantly governed by a single slow mode, while other modes correspond to faster fluctuations. The free energy minima identified by the model are stable and correspond well to previously reported metastable structures of the protein. We further demonstrate that these modes serve as efficient collective variables for enhanced sampling. Using the extracted modes as collective variables accelerates convergence of the free energy landscape by several orders of magnitude relative to standard approaches.

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Influence of Surface Dynamics on Ammonia Catalytic Decomposition Process