6th CCPBioSim/CCP5 Multiscale Modelling Conference

Programme

Monday Afternoon – https://ukri.zoom.us/j/99655158845
Tuesday Morning – https://ukri.zoom.us/j/91045594839
Tuesday Afternoon – https://ukri.zoom.us/j/92992230968
Wednesday Morning – https://ukri.zoom.us/j/92212955259

Day 1 - Monday 31 March 2025

12:00 – 13:20	Registration and Lunch
13:20 – 13:30	**Welcome / Introduction (Session Chair: Marc van der Kamp)**
13:30 – 14:05	Alessandro Troisi *High-throughput screening of polymeric semiconductors*
14:05 – 14:25	Kirill Zinovjev *QM/MM without QM: electrostatic machine learning embedding for enzymatic catalysis, ligand binding and more*
14:25 – 14:45	Anna Bui *Learning classical density functionals for ionic fluids*
14:45 – 15:05	Edoardo Donadoni *The impact of polymer coating on nanoparticles interaction with lipid membranes explored by coarse-grained molecular dynamics simulations*
15:05 – 15:35	**Coffee**
15:35 – 16:10	Chantal Valeriani *From active polymers' assembly to mechanical properties of a bacterial biofilm*
16:10 – 16:30	Carlo Fonte *From Electrons to Reactors: ab initio multi-scale simulation of methane oxidation over palladium oxide*
16:30 – 17:20	*Flash Talks A*
17:20 – 18:50	**Poster Session A - Odd Numbers**

Day 2 - Tuesday 1 April 2025

08:30 – 09:00	**Coffee (Session Chair: Charlie Laughton)**
09:00 – 09:35	Matthias Schmidt *Neural functionals and unexpected symmetries in statistical mechanics*
09:35 – 09:55	Marko Hanzevacki *Reaction mechanism of choline degradation by choline trimethylamine-lyase (CutC) revealed with QM/MM modelling*
09:55 – 10:30	Lorna Dougan *Current challenges and opportunities in translating the mechanical properties of biomolecules across lengthscales*
10:30 – 11:05	**Coffee**
11:05 – 11:40	Katarzyna Swiderek *Deciphering the role of protein electrostatic field in enzymatic catalysis: A case study of three distinct heterogeneous Proteasome □-subunits*

11:40 – 12:00	Tom Headen *Wide Q-range Total Neutron Scattering: Simulation Based Data-Refinement for Multi-Scale Systems*
12:00 – 13:30	**Lunch (Session Chair: Paola Carbone)**
13:30 – 14:05	Valentina Erastova *Let's talk about dirt: from environmental sorptive materials of Earth to biosignatures in Space*
14:05 – 14:25	Maria Grazia De Angelis *Multiscale and machine learning-assisted models for the design of materials supporting net zero, energy transition, and circular economy*
14:25 – 14:45	Mark Miller *Superselectivity and Nucleation in Biomolecular Condensates*
14:45 – 15:15	**Coffee**
15:15 – 15:50	Rebecca Wade *Multi-resolution molecular simulations to investigate the interplay between cytochrome P450 interactions, conformational variability and function*
15:50 – 16:10	Alberto Pérez de Alba Ortíz *Novel Bayesian approaches to biomolecular free-energy calculations: from ion-responsive polysaccharide rigidities to nanoplastic-induced protein dissociation*
16:10 – 17:00	*Flash Talks B*
17:00 – 18:30	**Poster Session B – Even Numbers**
19:00	**Conference Dinner**

Day 3 - Wednesday 2 April 2025

08:30 – 09:00	**Coffee (Session Chair: Stephen Cox)**
09:00 – 09:35	Benedetta Mennucci *Multiscale strategies to investigate light-responsive proteins*
09:35 – 09:55	Thomas Sayer *Small polaron transport in very large lattices with accurate numerics*
09:55 – 10:15	Kakali Sen *Structural and computational studies of an unusual crosslinked heme in Methylococcus capsulatus cytochrome P460*
10:15 – 10:35	*Jean-Marc Lude* *Molecular Density Functional Theory with Atomistic Dipolar Solvent to Study Pressure Effect on a Diels-Alder Reaction*
10:35 – 11:05	**Coffee**
11:05 – 11:25	Shakir Ali Siddiqui *Local Electric Field-Guided Redox Potential Tuning in de novo Proteins*
11:25 – 11:45	Maryna Bakumenko *Upscaling Simulations: Integrating Molecular Dynamics with Hydrodynamics*
11:45 – 12:20	Jochen Blumberger *Simulating Electronic Quantum Dynamics on the Nanoscale (10-100nm)*
12:20 – 14:00	**Lunch and Close**

Posters

Poster Number	Presenter Name	Poster Title
1	Baumhauer, Fiona	Predicting azeotropic phase diagrams using machine learned classical density functional theory
2	Brukhno, Andrey	Shapespyer: a Python driven toolchain for soft matter simulations
3	Chattopadhyay, Rajorshi	Development of polarizable force field for La3+ in Cl-bearing hydrothermal fluids
4	Doveiko, Daniel	Binding Energy Calculations of Anthracene and Rhodamine 6G H-type Dimers: A Comparative Study of DFT and SMD Methods
5	Epstein, Alexander	Understanding Hydrophobicity in Complex Geometries via Classical Density Functional Theory
6	Fairchild, Connie	A Minimal Model for the Frequency-Dependent Conductivity of Ionic Liquids
7	Findlay, Elliot	Modelling Soil-release Polymers on Fabric Surfaces: Multiscale Insights from Dissipative Particle Dynamics and Enhanced Sampling MD Simulations
8	Fitkin, Arielle	A computational investigation of metal-organofluorine interactions and their role in selective metal deposition
9	Freeman, Colin	Mineral Control over Molecular Binding and Decay
10	Galappaththi Guruge, Amali	Computational insights into structural changes in PEODT:PSS interfaced with water
11	Gopalakrishna Rao, Aditya	Multiscale simulations of the mechanism of a de novo designed Diels Alderase photoenzyme catalysing [2+2] cycloadditions: implications for photobiocatalyst design
12	Hayton, John	Silver Iodide in Water – A Machine Learned Interatomic Potential with Electrostatics
13	Hodala, Aydin	The effect of aggregation on the pKa of oleic acid
14	Jia, Hengjian	Discovering Blood Brain Barrier Permeable Compounds with Cliques Descriptors
15	Igaev, Maxim	Microtubule dynamics are defined by conformations and stability of clustered protofilaments

16	Kanagarajan, Ajeeth	Negative Chemotaxis of polymeric vesicles against lactic acid concentration gradient
17	Kazmierczak, Magdalena	Machine learning potentials for accurate and efficient multiscale enzymatic Diels – Alder reaction modelling
18	Lei, Li	Coarse-grained investigation of the adsorption behaviour of antibodies at water–hexadecane interfaces
19	Liu, Yufeng	Prediction of rhamnolipid partitioning into lipid bilayers using coarse-grained molecular dynamics with the Martini 3 force field
20	Meadows, James	Controlling Polymorph Crystallisation Using Structured Ternary Fluids
21	Meulemans, Arne	Organic Thermoelectric Polymers: atomistic modelling of semicrystalline P3HT
22	Morado, Joao	Enhancing Electrostatic Embedding for ML/MM Free Energy Simulations
23	Morgan, Liam	Understanding the Behaviour of Hole States for Copper Substitutionals in MgO
24	Novi Inverardi, Giovanni	Structural and dynamical assessment of the adsorption of silica oligomers on biomolecules via Molecular Dynamics
25	Ramos, Carlos	Capturing complexity in enzyme catalysis: Multidimensional Free Energy Landscape Explorations Using Multiscale Methods to Fight Infection Diseases.
26	Sahnoune, Meriem	Coarse-grained modeling of insulin adsorption on plasticized polyvinyl chloride surfaces
27	Thomas, Dominic	Understanding electrochemical interfaces with neural functional theory
28	Tomlinson, Emma	Understanding DNA-Protein Interactions in Eukaryotic Topoisomerases through atomistic molecular
29	Underhill, Juno	Spectral tuning in a de novo riboflavin protein
30	Yang, Chao-Yu	FibrilGen: a program to template cross-β nanostructures at the atomic level

31	Ymeraj, Matilda	Structure-based virtual screening targeting APSR: exploring covalent inhibitors against Pseudomonas
32	Zhang, Xibei	Transforming Tuberculosis Care: Rapid Accurate and Reliable Computer-Based Prediction of Drug Resistance to Guide Targeted Treatments
33	Zhou, Fulu	Applicability of the Thermodynamic and Mechanical Route to the Young Equation for Rigid and Soft Solids: A Molecular Dynamics Simulations Study of a Lennard-Jones System Model
34	Donadoni, Edoardo	Characterizing graphene biointeractions: coarse-grained modeling of ion binding, small molecule adsorption and protein corona formation
35	Güven, Jasmin	Protocols for free energy predictions for beta-lactamases: insights from cross-class inhibitors

QM/MM without QM: electrostatic machine learning embedding for enzymatic catalysis, ligand binding and more

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Multiscale QM/MM potentials allow simulations of large systems by combining quantum mechanics (QM) and molecular mechanics (MM) but are limited to short timescales due to computational costs. This issue could be solved by employing machine-learning (ML) potentials that, in principle, offer QM accuracy at a fraction of the computational cost. However, ML potentials are generally unable to describe the interaction between ML and MM parts, making their integration into QM/MM frameworks challenging.

A possible solution to this problem is to train a separate ML model that calculates the *in vacuo* energy of the QM region and its interaction with the MM environment (embedding). This "electrostatic ML embedding" (EMLE) scheme [1] learns from the atomic properties of the QM system in the gas phase and employs analytical models for electronic density and induction, eliminating the need for QM/MM energies in training.

We present how EMLE scheme enables ML/MM simulations with arbitrary ML potentials using existing QM/MM codes [2]. ML/MM molecular dynamics allows the study of various processes in condensed phases at DFT/MM level with only a fraction of the associated computational cost. To showcase the methodology, we apply ML(EMLE)/MM to conformational sampling of 3-methylindole in aqueous solution [3], calculation of the binding free energy profile for a ligand bound to DNA G-quadruplex, and prediction of the catalytic effect of chorismate mutase. In all cases, ML(EMLE)/MM provides results close to DFT/MM reference, outperforming MM and semiempirical QM/MM potentials.

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Learning classical density functionals for ionic fluids

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Owing to their importance across both science and technology, developing accurate yet manageable theoretical descriptions of electrolyte solutions and ionic liquids has challenged scientists for over a century. The difficulties arise from the fierce competition between the strong, long-ranged Coulombic interactions and steric repulsions at shorter range, which is completely missing in traditional Debye-Hückel and Poisson-Boltzmann theories. While classical density functional theory (cDFT) in principle offers an exact statistical mechanical framework for this problem, the approximations inherent to existing functionals have limited its applicability, pushing researchers to rely on costly molecular simulations.

In this work [1], we generalize a recently proposed machine learning (ML) approach [2] for representing the exact free energy functional of "simple liquids" to ionic fluids. Our approach solves the critical problem of incorporating non-local effects within the ML framework by leveraging the connection between cDFT and local molecular field theory. The resulting ML-based cDFT functional to be applied to much larger systems than those in the training set, quantitatively captures simulation data and ensures thermodynamic consistency. Our work opens a new avenue for studying ionic fluids and electrolyte solutions, not just by existing practitioners of cDFT, but also by those relying on molecular simulations. Furthermore, this work represents a critical step in evolving cDFT from a tool typically used in soft matter—where interaction potentials are often simpler—into a robust framework for chemical physics, where more complex potentials, such as those for ions and water, are common.

References

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The impact of polymer coating on nanoparticles interaction with lipid membranes explored by coarse-grained molecular dynamics simulations

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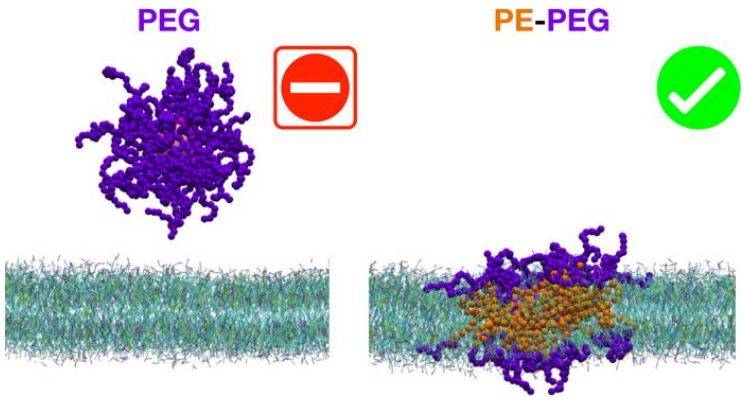
Nanoparticles' (NPs) permeation through cell membranes, whether it occurs *via* passive or active transport, is an essential initial step for their cellular internalization. The NPs' surface coating impacts the way they translocate through the lipid bilayer and the spontaneity of the process. Understanding the molecular details of NPs' interaction with cell membranes allows the design of nanosystems with optimal characteristics for crossing the lipid bilayer: computer simulations are a powerful tool for this purpose. In this study [1], we have performed coarse-grained molecular dynamics simulations and free energy calculations on spherical titanium dioxide NPs conjugated with polymer chains of different chemical compositions. We have demonstrated that the hydrophobic/hydrophilic character of the chains, more than the nature of their terminal group, plays a crucial role in determining the NPs' interaction with the lipid bilayer and the thermodynamic spontaneity of NPs' translocation from water to the membrane. We envision that this computational work will be helpful to the experimental community in terms of the rational design of NPs for efficient cell membrane permeation.



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From active polymers' assembly to mechanical properties of a bacterial biofilm

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Active filaments comprise systems in which a polymer is out-of-equilibrium by the action of fuel consuming units, such as micron-size flagella or millimetre-size worms. Particle-based models for active filaments, called ''active polymers'', include tangential active polymers [1,2,3] where the direction of the self-propulsion is parallel to the backbone tangent or a collection of active Brownian particles with no correlation along the backbone (active Brownian polymers) [4,5].
We have recently shown that in two dimensions active bivalent Brownian particles assemble into polymeric chains [6]. Interestingly, these chains can assemble into functional structures such as spinning spirals YY, as observed in suspensions of active Brownian polymers.
As expected, when explicitly considering hydrodynamics, the structural behaviour of active polymers if affected, even at the single chain level [7].

On the other side, one could consider polymers produced by bacteria, such as *E coli* or *Pseudomonas fluorescens*. These species are known to produce exopolysaccharides, that characterise the mechanical features of bacterial biofilms. Simulating these systems is quite challenging, due to their complexity and to the fact that bacterial biofilms span several times and length scales.
We have recently presented a mesoscale numerical model [8] that allows to study structural and mechanical properties of bacterial biofilms [9].

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From Electrons to Reactors: *ab initio* multi-scale simulation of methane oxidation over palladium oxide

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Heterogeneous catalysis, in practical applications, is an inherently multi-scale phenomenon. Multi-scale modelling aims to tackle the "grand challenge" of simulating catalytic processes by bridging atomic, molecular, pore, and reactor scales. However, it brings substantial challenges due to the complexity and diversity of phenomena involved, combined by the difficulties in aligning differences in temporal and spatial scales and handling the computational demands across each model layer.

Within the ReaxPro H2020 project, Johnson Matthey developed a multiscale workflow for catalytic methane combustion over palladium oxide. This work describes the construction, application, and outcomes of a fully *ab initio* multiscale simulation of catalytic methane oxidation over palladium oxide and doped catalysts within a structured (coated monolith) reactor. The simulation workflow spans the electronic and atomic, up to reactor scales, integrating multiple simulation techniques and software.

Electronic structure simulations were carried out using the GPAW[1] Density Functional Theory (DFT) package, with a plan-wave basis set and the BEEF-vdW functional. Atomic scale optimisation, transition state searching, and vibrational analysis applied routines in the Atomic Simulation Environment (ASE)[2]. The image-dependent pair potential method was applied for interpolation of intermediate images as input to climbing image nudged elastic band transition state searching algorithm. Vibrational analysis used a finite displacement method and the resulting modes derived by the method of Frederiksen[3].

Custom Python scripts were used to develop a microkinetic model based on DFT-derived data was processed, providing reaction rates for each elementary step of the methane oxidation reaction mechanism. Effective diffusivity for gas transport within the washcoat porous media was estimated from 3D porous structures obtained via FIB-SEM and digitally reconstructed. To build a continuum model of the monolith reactor, the kinetic model was coupled with heat and mass transport equations. This approach included both idealised plug-flow models and detailed reactive CFD simulations (using CatalyticFOAM[4]), to describe gas transport and reaction in the monolith under varying operating conditions.

The developed models were validated against experimental data collected through different reactive characterisation techniques. Model predictions demonstrated reasonable agreement with experimental results without any experimental fitting of parameters, highlighting the workflow's potential for tackling the complexities inherent to industrial catalytic processes.

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Neural functionals and unexpected symmetries in statistical mechanics

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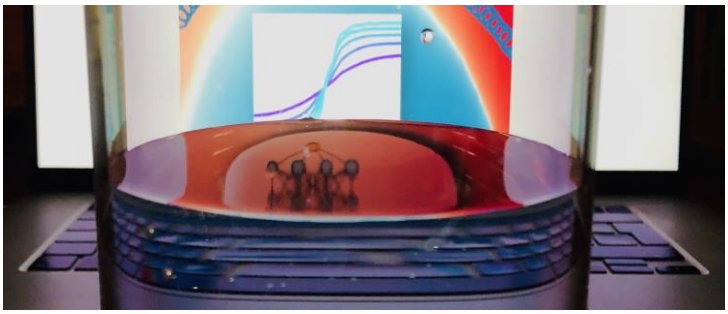
I give an overview of very recent progress in the statistical mechanics of spatially inhomogeneous many-body systems in equilibrium and with flow. Using neural functionals offers access to efficient machine-learned representations of density and power functional relationships [1-4]. The required training data stems from simple particle-based simulation setups. Straightforward training then yields functionals that allow one to investigate efficiently a wide array of physical phenomena not encountered during training, such as multi-scale problems [1, 2] and phase coexistence [2] (see illustration). The method leverages powerful functional automatic differentiation and numerical functional line integration together with the functional structure of statistical mechanics [1-5]. Thereby functional invariances generate exact Noether force and hyperforce sum rules that allow one to carry out consistency checks and to develop smart sampling algorithms. The sum rules follow from an hitherto unrecognized shifting gauge invariance of statistical mechanics [5]. (With contributions from: Florian Sammüller, Johanna Müller, Sophie Hermann, Daniel de las Heras,



Stefanie M. Kampa, and Robert Evans.)

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Reaction mechanism of choline degradation by choline trimethylamine-lyase (CutC) revealed with QM/MM modelling

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Choline trimethylamine-lyase (CutC), a glycyl radical enzyme (GRE) found in the human gut microbiome, plays a pivotal role in cleaving the C-N bond of choline, an essential nutrient, to produce trimethylamine (TMA) and acetaldehyde [1]. CutC has emerged as a critical therapeutic target due to its involvement in TMA production, which is subsequently converted to trimethylamine-*N*-oxide (TMAO) in the liver. TMAO has been implicated in various human diseases, including colorectal cancer (CRC), non-alcoholic fatty liver disease, cardiovascular disorders, atherosclerosis, chronic kidney disease, type 2 diabetes, and trimethylaminuria (fish odour syndrome). Understanding the mechanism of CutC is therefore crucial for developing potent inhibitors to address these health concerns.

In this study, we present a computational modelling approach to elucidate key aspects of the CutC mechanism. Our investigation begins by leveraging state-of-the-art protein structure prediction models, such as AlphaFold and Chai-1, to gain insights into the activation protein-protein complex and protein-ligand binding interactions in GREs.

We then conducted atomistic molecular dynamics (MD) simulations to examine the conformational behaviour of choline within the CutC active site. These simulations revealed the critical influence of hydrogen bonding and electrostatic interactions in facilitating the initial *pro*-S hydrogen abstraction. We employed quantum mechanics/molecular mechanics (QM/MM) methods to compute the reaction mechanism [2]. The performance of three functionals (B3LYP, ωB97X-D3, and M06-2X) was tested against DLPNO-CCSD(T). Our findings suggest that choline cleavage likely proceeds *via* TMA-migration, leading to carbinolamine formation. We identified two distinct pathways: one with a high activation energy barrier of 21 kcal mol^{-1}, and the other with a more feasible barrier of 14.6 kcal mol^{-1}, which is consistent with experimental activation kinetic parameters. To further elucidate the molecular basis for differential binding affinities, we explored the interactions of both the choline substrate and carbinolamine product with CutC using free energy perturbation (FEP) simulations.

Our ongoing research is focused on comparing CRC-associated CutC sequences and isolating the enzyme in the laboratory for further studies. This work promises to provide valuable insights into the structural and functional variations of CutC across different microbial species, potentially leading to the development of targeted inhibitors for therapeutic applications.

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Deciphering the Role of Protein Electrostatic Field in Enzymatic Catalysis: A Case Study of Three Distinct Heterogeneous Proteasome **β**-Subunits

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The origin of the enzyme's powerful role in accelerating chemical reactions is one of the most critical and still widely discussed questions. It is already accepted that enzymes impose an electrostatic field onto their substrates by adopting complex three-dimensional structures, therefore, the preorganization of electric fields inside protein active sites has been proposed as a crucial contributor to catalytic mechanisms and rate constants enhancement, as recently confirmed in our laboratory.[1] Herein, we focus on three catalytically active β-subunits of 20S proteasome with low sequence identity (~30%) whose active sites, although situated in an electrostatically miscellaneous environment, catalyse the same chemical reaction with similar catalytic efficiency. Our in-silico experiments reproduce the experimentally observed equivalent reactivity of the three sites and show that obliteration of the electrostatic potential in all active sites would deprive the enzymes of their catalytic power by slowing down the chemical process by a factor of 10^{35}. To regain enzymatic efficiency, besides catalytic Thr1 and Lys33 residues,[2] the presence of aspartic acid in position 17, and aqueous solvent is required, proving the electrostatic potential generated by the remaining residues insignificant for catalysis. Moreover, it was found that the gradual decay of atomic charges on the Asp17 strongly correlates with the enzyme's catalytic rate deterioration, as well as with a change in the charge distributions due to introduced mutations. The computational approach described here could aid in identifying key residues involved in catalysis across other biomolecular systems, potentially contributing to the design of enzyme-inspired synthetic catalysts.[3]

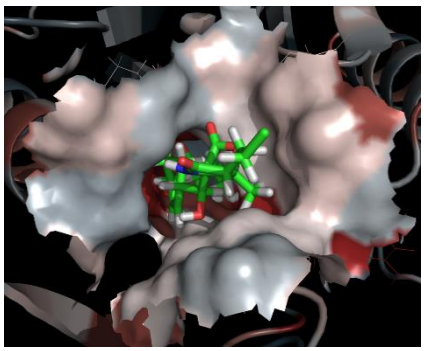

Figure 1: Active site of 20S proteasome β5 subunit with bound SalA compound.

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Wide Q-range Total Neutron Scattering: Simulation Based Data-Refinement for Multi-Scale Systems

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The Near and InterMediate Range Order Diffractometer (NIMROD) at the ISIS Neutron and Muon Source provides a unique experimental insight into multiscale disordered systems – effectively combining the usually separate techniques of total scattering and small-angle neutron scattering. Over the last couple of decades "Empirical Potential Structure Refinement" (EPSR) techniques have become the standard approach for analysing total neutron scattering data on liquid systems. In essence the method starts with a classical simulation of the system of interest, the difference between experimental and simulated scattering is then used to derive an additional "empirical" potential that pushes the simulation towards matching the data [1,2]. This has been successfully deployed on many molecular liquids, particularly those containing hydrogen, where isotopic substitution can be used to maximise the number of constraining datasets [3].

The development of NIMROD, however, presents a computational challenge as the data cover correlations from sub Angstrom to 300Å. We will present the progress to date, where the system of interest pushes the boundaries of these simulation based analysis methods, allowing a unique multiscale understanding of structure in systems such as carbon nanotube solutions [4], confined fluids [5], soft matter [6] and biochemical systems [7]. Finally, we will look to the future and discuss possible methods to bridge the gap and provide self-consistent multiscale refinement of the full lengthscale range probed by NIMROD by combining Coarse-Grained and atomistic simulation [8].

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Multiscale and machine learning-assisted models for the design of materials supporting net zero, energy transition, and circular economy

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Advanced materials play a critical role in achieving Net Zero targets and advancing the energy transition and circular economy. In this talk, we will explore the use of polymeric and composite materials across various applications. These include CO_2 capture, gas purification, healthcare, biodegradable packaging and hydrogen storage and transport. The development and refinement of reliable modeling tools are crucial for designing new materials or enhancing existing ones to ensure efficient performance and minimal energy use in separation processes, achieve zero waste in packaging, and reduce risks in handling compressed hydrogen.

This presentation will demonstrate how models that span multiple scales-from atomistic to finite element and continuum thermodynamics-can be wisely integrated to boost predictive accuracy and computational efficiency. We will also introduce new hybrid ML-Physics methods (Fig. 1), designed for predicting the behaviour of high-performance polymer membranes, transferring the knowledge from small molecules to macromolecular systems. [4-5].

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Superselectivity and Nucleation in Biomolecular Condensates

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Proteins and nucleic acids can condense into droplets in biological cells by processes resembling liquid–liquid phase separation. These droplets, or "membraneless organelles", serve a variety of essential functions, ranging from response to physical or chemical stress, to regulating concentrations and chemical processes within the cell. Open questions on biomolecular condensates involve molecular-level interactions as well as quasi-bulk material properties, requiring analysis at multiple length scales. Here I will outline two contrasting phenomena that we tackle with coarse-grained molecular modelling and a continuum description, respectively.

Typical condensates are many-component mixtures of multivalent biopolymers, interacting both at specific binding sites and through generic attraction. At planar interfaces, multivalent polymers and functionalised colloids can exhibit "superselectivity" [1], i.e., a sharper binding-unbinding transitions than monovalent species. Using Monte Carlo simulations of a highly idealised model of multivalent species, we explore whether biomolecular condensates can act as porous, three-dimensional hosts that exploit superselectivity to recruit and expel other species, thereby fine-tuning their concentration in the cell. We find that molecular crowding is an essential ingredient to achieve superselectivity in three dimensions [2].

Biomolecular condensates can also interact with and mediate interactions between membrane-bound subcellular structures. Membranes are flexible and deform in response to contact with the condensates. I will describe a continuum model for analysing the heterogeneous nucleation of a droplet on a flexible membrane, showing that there are two branches to the free energy profile in which the droplet is partially or fully wrapped by the condensate, respectively. These distinct morphologies raise the possibility of multiple nucleation pathways.

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Multi-resolution molecular simulations to investigate the interplay between cytochrome P450 interactions, conformational variability and function

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Mammalian class II cytochrome P450 (CYP) enzymes are membrane-bound and rely on NADPH-cytochrome P450 reductase and cytochrome b5 for the provision of electrons for catalysis. We have employed multi-resolution molecular dynamics simulations to investigate the membrane, protein, substrate, product, and solvent interactions of three CYPs: CYP 1A1, CYP 2B4 and CYP 17A1. From these simulations, we compared the structural ensemble, active site accessibility and electron transfer properties of these three CYPs when anchored in a membrane and when complexed with redox proteins. Using the simulation data and quantum mechanical calculations, electron transfer rates and pathways were computed and compared for different protein complexes, revealing sequence-dependent pathways. The results throw light on the complex interplay between CYP conformational flexibility and ligand binding, the determinants of electron transfer rates, and the modulatory roles of the redox proteins.

Novel Bayesian approaches to biomolecular free-energy calculations: from ion-responsive polysaccharide rigidities to nanoplastic-induced protein dissociation

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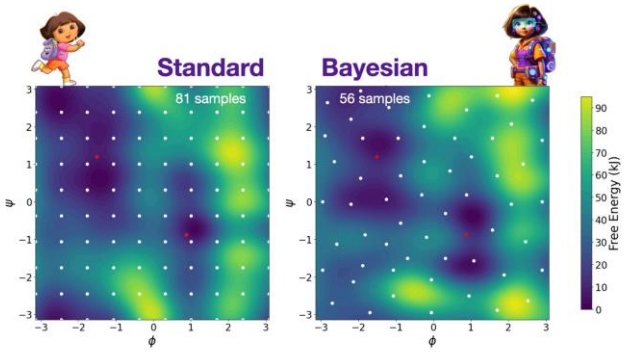
To dissect and control biomolecular processes, it is essential to map their free-energy landscape. This landscape reveals metastable states and interconnecting paths—projected onto key atomistic descriptors, i.e., collective variables (CVs)—which are crucial to understand chemical, conformational or phase transitions. Since most interesting processes are rare events within affordable computational timescales, multiple enhanced sampling methods have been introduced. Many of these methods exert biasing potentials to drive the system into usually unsampled regions. The average biasing force can be used to numerically integrate an approximation of the free-energy landscape. However, determining where to set the biasing potentials can be daunting, particularly for complex systems involving many CVs. To tackle this, we employ Bayesian quadrature as a method to estimate the value of an integral, i.e., the free energy, based on iteratively selecting the most informative gradient samples, i.e., forces, based on a noise-tolerant probabilistic model. This approach can either explore the landscape by reducing the overall uncertainty or exploit it by searching for minima or maxima. We demonstrate the robustness of this approach across novel applications to relevant biomolecular systems. We predict the ion-responsive bending free energy, i.e., persistence length, of hyaluronan, a ubiquitous polysaccharide whose mechanical properties are crucial in cancer and osteoarthritis development. Moreover, we predict the nanoplastic-induced dissociation free energy of vascular endothelial cadherin, a key junctional protein safekeeping endothelial integrity in animal arteries and veins. In both cases, our Bayesian approach efficiently reveals the impact of specific agents—ions or nanoplastics—on complex biomolecular function.



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Small polaron transport in very large lattices with accurate numerics

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Understanding charge and energy transport in materials with strong electron-nuclear coupling remains a fundamental challenge, often limited by finite-size effects and computational cost. We present recent advances that leverage algorithmic improvements and memory-based approaches to enable the exact simulation of polaron formation and transport, with application to the dispersive Holstein model [1]. By extending generalized master equations to incorporate finite memory in both time and space [2], we unlock the ability to simulate arbitrarily large systems from the dynamics of small lattices in both 1 and 2 dimensions, presenting converged results from almost 1000 sites with 100s of picoseconds of quantum dynamical evolution.

These advances provide new insights into the links between nonequilibrium relaxation, anomalous transport, and widely used formalisms such as Green-Kubo relations and Drude-Smith conductivity [3]. We demonstrate how polaron transport approaches diffusive behaviour only asymptotically in time and space and show how anisotropy can induce localization [4]. Our results establish a direct link between microscopic interactions and macroscopic transport, offering new interpretative tools for mapping experimental measurements of polymers and transition metal oxides directly onto a lattice model [3].

Although we work with numerically exact numerics on model systems, the memory formalism is completely general and not tied to a particular dynamical method. Extension to correlation functions derived from semiclassical approaches, including those used in atomistic simulations [5], offers tantalizing prospects to both access the hydrodynamic limit while also cutting down the time costly trajectory method averaging requires to converge the key observables.

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Structural and computational studies of an unusual crosslinked heme in *Methylococcus capsulatus* cytochrome P460

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Cytochromes P460, a key enzyme in the global nitrification pathway, oxidise hydroxylamine (NH_2OH) to nitrous oxide (N_2O) and contain as their active site an unusual catalytic c-type heme where the porphyrin is crosslinked to the protein via a lysine residue in addition to the canonical cross links from cysteine residues. Understanding how bacteria use CytP460 to convert NH_2OH to the greenhouse gas N_2O is of major agricultural and environmental significance and such crosslinks play a role in dictating the activity of this enzyme.

Prior structural characterisation of CytP460 from *Nitrosomonas europaea*[1] and *Methylococcus capsulatus* (Bath, *Mc*P460)[2] clearly shows the existence of a single crosslink between the N atom of a lysine side chain and the heme porphyrin. In our current combined experimental and computational work, we describe the evidence for a novel double crosslink between lysine and heme in *Mc*P460[3]. To understand the complexities of this enzyme system we applied high resolution structural biology approaches at synchrotron and XFEL sources paired with QM/MM molecular simulations[4] and prediction of UV-Vis spectra. All possible chemical species associated with the crosslink were first modelled via QM/MM ground state optimisation using DFT as the QM code using D3-B3LYP functional via NWChem integrated within Py-Chemshell[5]. These calculations were followed by spectral simulations at the same QM/MM level to ascertain the electronic structure of this unique double crosslinked species enabling the prediction of experimentally observed electronic absorption spectra. The spectral calculations were carried out using time-dependent DFT (TD-DFT)[6] using range separated functional, CAM-B3LYP, within ORCA that was integrated with Py-Chemshell. All the calculations used def2-TZVP for the Fe and def2-SVP for all other atoms. Our work demonstrates the feasibility of a double crosslink in *Mc*P460 and provides an opportunity to showcase how simulations can interact with experimental structures to provide insights into the structure of such a complex enzyme.

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Molecular Density Functional Theory with Atomistic Dipolar Solvent to Study Pressure Effect on a Diels-Alder Reaction

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High-pressure chemistry offers innovative solutions to synthetic challenges, enabling access to novel products and providing deeper insights into reaction mechanisms. Theoretical and computational approaches to calculating solvation free energy are central to these studies but present significant challenges. Achieving a balance between computational efficiency and accuracy requires precise descriptions of solute, solvent, and solute-solvent interactions [1].

In this context, classical density functional theory (cDFT) of fluids, particularly its molecular extension (MDFT), has emerged as a powerful tool for studying solvation effects in complex systems [2]. MDFT allows for the treatment of molecular, rather than purely atomic, fluids and facilitates the computation of solvation free energies at a fraction of the cost of explicit molecular dynamics simulations. Moreover, cDFT provides detailed structural information about the solvent and the flexibility to capture thermodynamic properties under varying pressure conditions, making it highly suited for high-pressure studies.

In the present work, we have extended molecular density functional theory (MDFT) to study model solvents at high pressure, with a particular focus on addressing how chemical reactivity can be modified. Notably, we considered an example of a Diels-Alder reaction in model apolar and polar solvents. MDFT enables the calculation of solvation free energies for different chemical structures along the reaction pathway at various pressures. These values, combined with (electronic) density functional theory calculations providing energetic differences between reactants, transition states, intermediates, and products, allow us to obtain reaction free energy profiles over a wide pressure range (from ambient pressure to 1.5 GPa).

Special attention was given to the role of the solvent's dielectric response and its influence on reaction kinetics. The model successfully reproduces the experimental dielectric constant at intermediate pressures (0–0.2 GPa) and infers its increase at high pressures in the GPa range. The numerical findings align with experimental observations, demonstrating that the reaction is promoted by high pressures and that a trans/cis diastereoselectivity is induced in the product distribution. It is shown that electrostatic interactions play a major role in these findings. Furthermore, the experimentally observed relative insensitivity of activation volumes with respect to pressure appears to result from a compensation between packing and electrostatic effects.

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Local Electric Field-Guided Redox Potential Tuning in *de novo* Proteins

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Electric fields play a pivotal role in modulating the redox properties of enzymes by influencing the stabilization of charge-separated intermediates and the energetics of electron transfer.[1] Recent computational and experimental studies have demonstrated that local electric fields (LEFs) within protein active sites can fine-tune catalytic efficiency, via orienting it in specific manner.[2] Understanding how these LEFs influence reaction energetics is key to designing more efficient biocatalysts.[3] However, quantifying and engineering these effects in artificial enzymes remains a challenge.

Computational *de novo* protein design has reached a level of precision where atomistic control over biomolecular building blocks is increasingly routine.[4] However, the rational design of redox-active enzymes remains a significant challenge due to the complexity of fine-tuning cofactor interactions and catalytic function. The 4D2 helical bundle, rationally designed for heme binding, has now been strategically enginnered into m4D2 and e4D2, expanding its redox capabilities.[5] These metalloenzymes serve as robust and tuneable platforms for studying the interplay between electric fields, metal coordination, and redox activity. Recent computational simulations have demonstrated the feasibility of predicting redox potentials via fluctuation relations.[6] By leveraging computational tools and structural insights, we can engineer these proteins to modify their electrostatic environments, enabling precise control over their redox potentials.

In this study, we first investigate how external electric fields affect the redox potential of heme, observing significant shifts in its redox behaviour. Building on these findings, through MD and QM/MM simulations, we explore how the local electric fields (LEFs) within *de novo* metalloenzymes, such as 4D2, m4D2, and e4D2, align similarly to the external fields, influencing their redox properties. By leveraging this understanding, we proceed to translate these electric field effects through targeted mutations, systematically modifying the enzyme's active site to fine-tune its redox potential. While this is an ongoing study, the results thus far suggest that by modifying the local electrostatic environment, we can achieve predictable shifts in redox potential, paving the way for further optimization and expanding the scope of *de novo* enzyme design.

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Upscaling Simulations: Integrating Molecular Dynamics with Hydrodynamics

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Classical Molecular Dynamics (MD) simulations provide atomistic precision by solving Newtonian equations of motion and computing inter-particle forces. These simulations effectively capture macroscopic thermodynamic properties and microscopic features, such as radial distribution and autocorrelation functions. Despite advancements in computational power, MD simulations remain limited to nanometer-scale systems, making it challenging to model biologically relevant processes over micro- to millisecond timescales.

A promising solution is MD-continuum coupling, where part of the MD domain is replaced by a continuum (Hydrodynamic, HD) description. However, integrating these two frameworks presents significant challenges. This work builds upon Smith's approach [1], applying the Gaussian principle of least action to derive motion equations that ensure momentum conservation between MD and HD representations. The liquid system is treated as a two-phase mixture, combining Lagrangian (MD) and Eulerian (HD) descriptions of the same substance [2]. The transition between atomistic and continuum regions is governed by a parameter s ($0 \leq s \leq 1$), ensuring a seamless link between discrete and continuous representations through a Control Volume formulation.

To achieve consistent MD-HD coupling, a constraint force is introduced into the MD equations of motion, ensuring momentum conservation in the hybrid region. This constraint, derived from the Principle of Least Action and Gauss's principle, results in modified, constrained equations of motion that align with a reformulated Lagrangian framework. Notably, it is shown that the Principle of Least Action remains valid, as equations derived from Gauss's principle of least constraint and Gauss's principle itself are equivalent.
This approach provides a rigorous foundation for scaling up MD simulations, enabling more efficient modeling of complex liquid systems across multiple length and time scales.

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Simulating Electronic Quantum Dynamics on the Nanoscale (10-100nm)

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Many molecular processes that we try to model on our computers are localized in space: molecular adsorption, ligand binding, enzyme catalysis, electron transfer, photo-chemistry etc. This notion led to the development of the first, Nobel prize-winning multi-scale methodology: QM/MM, where only a small region of the system (the ``actor") is treated at a quantum mechanical level of theory and the rest (the ``spectators) at a more approximate level. The convenient distinction between actor and spectator can no longer be made for many functional processes in molecular materials: all molecules are potential actors and should be treated at a QM level. Examples include exciton diffusion and charge transport, the conversion of photons to charge carriers or the conversion of a temperature gradient to electricity. An additional complication in the modelling of these important processes is that one needs to go beyond the Born-Oppenheimer approximation and simulate the system well beyond the time scale that is typically required for non-adiabatic dynamics simulation of photochemistry - a worst-case scenario for the modeller.

In my talk I will present a non-adiabatic molecular dynamics simulation approach that we have developed to address these challenges[1,2,3]. Our method combines fast on-the-fly construction of the electronic Hamiltonian with decoherence-corrected fewest switches surface hopping satisfying to good accuracy desirable properties including energy conservation, internal consistency and detailed balance in the long-time limit. Importantly, it enables us to simulate the electronic quantum dynamics coupled to (classical) nuclear motion for truly nanoscale molecular materials (10-100 nm) and over about 10-100 ps. We will present a number of applications including charge[1,4] and thermoelectric[3] transport in molecular organic crystals as well as exciton diffusion[2] and dissociation of excitons to charge carriers at organic molecular interfaces[5]. We found that charge carriers and excitons form ``flickering" quantum objects that are ``half way" between waves and particles, diffusing within the material via a novel transient quantum delocalization mechanism[1-4]. Moreover, we found that owing to the delocalized nature of excitons they can dissociate to electrons and holes several nanometers away from the donor-acceptor interface[5] challenging the common wisdom of how charges are generated in organic solar cells. Implications of our results for materials design will be discussed.

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Predicting azeotropic phase diagrams using machine learned classical density functional theory

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An azeotrope is a mixture whose composition remains unchanged upon transition between liquid and vapour phases. As a result, these mixtures cannot be separated into their components via simple fractional distillation. Instead, azeotropic mixtures are often separated through the addition of a separating agent which alters the liquid volatilities sufficiently to allow for distillation. Alternatively, a separating agent may form one or more azeotropes with the individual components[1]. Designing effective methods for separation of azeotropic mixtures is thus critically dependent on an accurate understanding of azeotropic phase diagrams.

Grand-canonical Monte Carlo (GCMC) calculations and molecular dynamics simulations have previously been employed to predict azeotropic phase diagrams theoretically. However, these techniques are often complex and computationally expensive[2]. Classical density functional theory (cDFT) in combination with machine learning can provide an alternative route to equilibrium thermodynamic properties at a significantly reduced computational cost[3-5]. In the present work, thermodynamic properties of azeotropic systems are accessed through knowledge of the one-body direct correlation function. The relationship between density profiles and the one-body direct correlation function was established through machine learning using training data generated via GCMC simulations in the presence of varying external potentials. Here, the description of azeotropic systems through machine learning-assisted cDFT is discussed.

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Shapespyer: a Python driven toolchain for soft matter simulations

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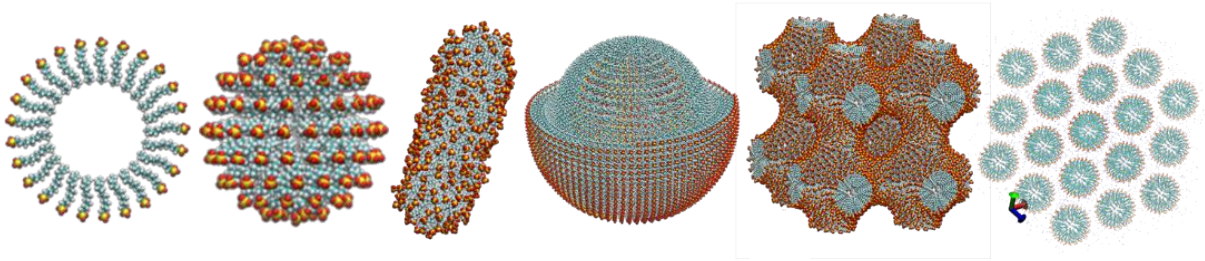
The Shapespyer project is a thriving collaboration between SCD, ISIS and Diamond (UKRI) under the overarching Ada Lovelace Centre (ALC) scheme, which supports and facilitates frontier interdisciplinary research by bridging between theoretical analysis, computer simulation and experimental studies. The primary goal of the project is to equip Small Angle Scattering (SAS) and Neutron Reflectometry (NR) experimentalists with seamless simulation and analysis workflows allowing for verification of theoretical conjectures about complex molecular nanoaggregates by comparison between experiments and detailed computer simulations. To this end, we have developed Shapespyer [1] - a Python-driven molecular structure generation API library with toolchains for simulation of multicomponent nanostructures ubiquitous in soft matter and biomolecular systems. Taking a set of template molecules as inputs (one per solute species), Shapespyer automatically generates nanoscale aggregates that can be further used as inputs for atomistic or coarse-grain molecular dynamics, including Martini and DPD, simulations. The simulations can be carried out on any computing platform, including heterogeneous HPC, e.g. Scarf, ARCHER2, Baskerville. The outcomes include equilibrated structures and trajectories that can be analysed and compared with data from appropriate experiments, e.g. SANS, SAXS, NR.
The supported molecular arrangements are shown below.



The supported post-simulation analyses include: (i) cluster classification and size distribution analyses, (ii) radius of gyration and its principal components, (iii) hydration layer and cavity occupation analyses, (iv) mass and neutron-scattering-length densities.

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Development of polarizable force field for La^{3+} in Cl-bearing hydrothermal fluids

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Rare Earth Elements (REEs) are strategically important group of elements with applications in critical fields like catalysis, electronics and green energy. In-depth understanding of the speciation and thermodynamics of REEs in high temperature (T) and high pressure (P) geochemical fluids are indispensable to constraining physico-chemical processes that lead to their mobilization and enrichment in the Earth's crust. The ability of fluids to mobilize the REEs depends on the chemical composition and the presence of suitable ligands such as chloride and fluoride.

In addition to experiments, Molecular Dynamics (MD) simulations offer an alternate methodology to investigate such systems particularly at T, P conditions not easily attainable in laboratories. The success of MD simulations depends on the accuracy with which interatomic forces are represented by the underlying interaction potentials. Ab Initio Molecular Dynamics simulations (AIMD) have been used to predict stability constants of various REE complexes in hydrothermal conditions [1]. However, AIMD simulations often suffer from significant finite time and size effects. Due to their much higher efficiency, classical force fields can overcome some of the shortcomings of AIMD while providing sufficient geochemical insights into fluid properties at hydrothermal conditions. The reliability and accuracy of classical force fields for simulations of aqueous electrolytes not only depend on the representation of ionic charge and size but also on the polarization of the charge densities of solvent and solute. Many different polarizable force fields exist, each having different representations of polarizability.

Here, we develop a new many-body Polarizable Ion Model (PIM) for La^{3+} in Cl-bearing hydrothermal fluids. The force field is fitted to snapshots of AIMD simulations of La^{3+} and Cl^- ions in water at hydrothermal conditions (773 K, 5 kbar) and includes an explicit treatment of atomic polarizabilities. We use Maximally Localized Wannier Functions (MLWFs) along with force and dipole matching techniques to fit the parameters of the potential [2]. Experimental and AIMD data (wherever available) are used to test the validity of the new potential by comparing structural and thermodynamic properties. We present association constants of La^{3+} complexes derived from MD simulations and compare our results against other non-polarizable pair potentials to establish the importance of atomic polarizabilities in solutions containing highly polarizable ions (Cl^-) and ions with high polarization power (La^{3+}).

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Binding Energy Calculations of Anthracene and Rhodamine 6G H-type Dimers: A Comparative Study of DFT and SMD Methods

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With the ever-growing need to study systems of increased size and complexity, modern density functional theory (DFT) methods can often encounter problems arising from growing computational demands. In this work, the applicability of steered molecular dynamics (SMD) in calculating binding energies of dimers was addressed and validated using DFT calculations by employing functionals from various rungs of Perdew's "Jacob's ladder" which classifies the functionals based on their accuracy in predicting exchange-correlation energy [1]. Since the dimerization of such complexes is driven mainly by π-stacking interactions, measurements of binding energies, especially in solutions, are experimentally demanding or even currently impossible, so computational estimates of the stability of dimers in solutions are irreplaceable [2, 3].

By conducting DFT calculations on both optimised and unoptimised anthracene and Rhodamine 6G (R6G) dimers and comparing the obtained results with SMD-predicted values, it was found that SMD predictions are in good agreement with the results obtained from hybrid DFT calculations. The average binding energies for optimized anthracene dimers were found to be 6.46 kcal/mol using DFT at ωB97X-D4/def2-QZVPP [4-6] compared to 7.64±1.61 kcal/mol predicted by the SMD. The binding energies for the R6G H-type dimer were 17.48 kcal/mol and 19.02±2.22 kcal/mol, respectively. The study also revealed that SMD tends to overbind dimers due to the lack of explicit terms accounting for electron-electron interactions in MD force fields. It is anticipated that the presented method can be applied to more complex dimers, potentially accelerating the calculations of binding energies. The proposed method is not intended to replace conventional DFT or *ab initio* calculations entirely but rather to complement them by providing preliminary binding energy estimates with significantly lower computational costs. Finally, this work reinforces the quality of the CHARMM36 FF [7].

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Understanding Hydrophobicity in Complex Geometries via Classical Density Functional Theory

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Hydrophobic forces are ubiquitous in nature and have applications in a broad range of fields, from desalination to drug design[1]. Despite this ubiquity, there are still fundamental gaps in our understanding of the multiscale nature of the hydrophobic interaction. While detailed experimental studies have been performed, such as atomic force microscopy (AFM) and surface force apparatus measurements, it remains challenging to connect experimental observations to an atomistic model of the solvent[2]. For example, when using molecular dynamics simulations to connect mesoscopic AFM experiments to the molecular length scale of water, most studies rely on the single tip approximation, where the AFM tip interacts with the material surface through a single adsorbed water molecule[3]. This approximation is useful for molecular dynamics simulations, where modeling tip asperities on larger length scales becomes prohibitively expensive, but is a significant simplification of complex geometries and cannot model the effects of surface defects or tip curvature. Experimental work has also observed widely varying hydrophobic interactions as a function of surface roughness[4,5]. With this variation arising from surface features ranging from 10s-100s of nanometers, atomistic molecular dynamics simulations cannot capture the molecular level origins of the differing hydrophobic interactions.

Instead of the typical molecular dynamics approach, we use recent advancements in classical density functional theory (cDFT)[6] to understand how surface features in both the AFM tip and the material surface affect solvent structure and hydrophobic interactions. In this poster, we discuss multiscale modeling of water in complex systems up to 100s of nanometers via an implementation of cDFT in three-dimensional systems with arbitrary geometries.

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A Minimal Model for the Frequency-Dependent Conductivity of Ionic Liquids

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The conductivity spectrum of an ionic liquid contains a wealth of information regarding the microscopic response and relaxation processes that govern how it behaves. However disentangling the molecular origins of the features we see in these macroscopic spectra is a significant challenge. In this work we look to address this by constructing a set of increasingly complex analytical models for the mechanisms of charge transport within bulk ionic liquids. More specifically we focus on explicitly including molecular-level phenomena such as the Debye-Falkenhagen effect.

Building upon the most simple model, Debye relaxation, we look to increase the complexity incorporated into the memory of the system. The memory function contains all the information regarding how each ion interacts with its environment and hence dictates its contribution to the bulk conductivity. Proposing a mathematical form for the memory function is equivalent to proposing a complete model of the transport [1]. By starting from a minimal form and gradually increasing its complexity, we simultaneously discover how complicated our physical picture needs to be, and how complicated it can justify being. An analysis of the moments of these analytical forms for the conductivity has provided a method to extract multiple charge transport timescales from these spectra. The validity of the models is tested by their ability to reproduce features seen in conductivity spectra from molecular dynamics simulations. We also show how they can be used to inform analysis of other experimentally accessible spectra (dielectric relaxation spectroscopy, electrochemical impedance spectroscopy), opening the door for direct access to mechanistic detail from macroscopic measurements.

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Modelling Soil-release Polymers on Fabric Surfaces: Multiscale Insights from Dissipative Particle Dynamics and Enhanced Sampling MD Simulations

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Soil release polymers (SRPs) are a class of funcitonal polymers found in modern detergent formulations, whose primary operations are to modify synthetic fabric surfaces to allow water transport and to prevent the redeposition of oil-based soil particles during the wash cycle.[1] In this work, SRPs are modelled at fabric surface-water interfaces using dissipative particle dynamics (DPD) and Hamiltonian replica exchange molecular dynamics (H-REMD), the latter of which lowers energy barriers to allow us to explore conformations that are outside of the timescale of conventional MD.[2]

DPD is a mesoscale, coarse-grained modelling technique, that falls on length and time scales somewhere between atomistic simulations and macroscale simulations.[3] This makes it ideal for observing mesoscale phenomena at longer timescales, while still retaining some chemical detail. We describe the process of parametrising and validating these simulations and explore how changes in polymer structure affect surface binding and solution aggregation. Combined with enhanced sampling methods (H-REMD and umbrella sampling), we can accurately extract free energy curves to gain a quantitative understanding of the surface-polymer interactions.[4] By collaborating with synthetic chemists and industry partners, this work will help in screening for more effective greener candidates.

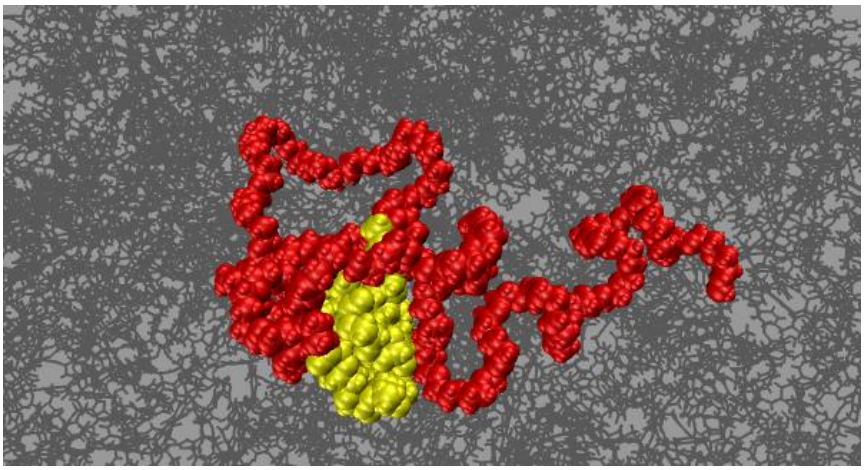

Figure 1. SRP on a polyurethane surface modelled using the H-REMD. Hydrophobic core (yellow) binds to the surface (grey) as a ball, while the PEG arms (red) stretch out.

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A computational investigation of metal-organofluorine interactions and their role in selective metal deposition for next-gen photovoltaics

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Controlled deposition of metals onto a given surface is a slow and costly process, but is essential for electronics and photovoltaics. Recently, a novel method for selective deposition has been discovered by our experimental collaborators, the Hatton group, which uses a thin layer of specific organofluorine compounds to prevent metal atoms from being adsorbed onto a surface. We leveraged density functional theory to investigate the nature and strength of the interaction between various metals and organofluorines, and to determine the extent to which the direct interactions between a metal atom and an organofluorine molecule affect this process of selective deposition. In particular, we found that the condensation of zinc onto a surface can be made highly selective, as its interactions are extremely weak and dominated by dispersion forces.

These are the first steps in understanding the complex interplay between the metal-organofluorine interaction strength and the polymer-polymer intermolecular interactions. Expanding our knowledge of these interactions, which allow specific organofluorines to prevent metal condensation on surfaces, will enable further development of this new method of fabricating electrodes for photovoltaics.

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Mineral Control over Molecular Binding and Decay

The interactions between molecules and material surfaces is important in a range of industries. Molecular adhesion can lead to fouling of material surfaces that can impede function and damage the material leading to failure of equipment. Molecular adhesion is used by bacteria and viruses to bind to surfaces leading to biofilm formation which in turn spreads infections and disease. Molecular-material interactions are even important in the fields of archaeology and paleontology. Much of our understanding in these fields come from ancient proteonomics where molecules are extracted from fossils, archaeological sites and tools. These molecules give us clues to the diet and lifestyle of early humans and even older species. This information is however, reliant on us understanding the decay processes of these molecules so we can accurately identify their origin.

I will present a range of atomic level simulations of molecular systems in aqueous environments in the presence of mineral surfaces. These simulations will examine how we can identify the binding processes at these surfaces and how that might lead to the breakdown of the molecule. We then examine how molecular structure and water dynamics at mineral surfaces will alter the presence of these motifs and potentially alter the decay process extending or shortening the lifetime of the molecule.

Computational insights into structural changes in PEODT:PSS interfaced with water

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In many bioelectronic applications, conductive polymers interface with biological tissues or fluids to sense, monitor or stimulate biological signals [1, 2], where water is the predominant component. In this study, we used molecular dynamics simulations to investigate the interface between the conductive polymer poly(3,4-ethylenedioxythiophene):polystyrene sulfonate (PEDOT:PSS) and water, focusing on morphological changes in PEDOT lamella crystallites within both PEDOT-rich and PSS-rich phases due to water permeation [3]. Our findings reveal that water permeates the polymer through a complex, interconnected network, with no significant difference in pore size distribution or water intake between PEDOT- and PSS-rich phases. These channels may correspond to pre-formed pores in the dry PEDOT:PSS film, as suggested by Sedghamiz *et al.*, [4] which become water filled upon hydration. Water permeation expands these pores, resulting in a broad range of pore sizes in the wet film. This leads to the formation of relatively smaller, less ordered PEDOT lamella crystallites in the wet film compared to the dry film, while also enhancing the alignment of PEDOT chains within each crystallite. Additionally, the inter-lamella distance between crystallites is significantly greater in the wet film. We argue that these structural changes in PEDOT lamella crystallites contribute to the experimentally observed reduction in conductivity of PEDOT:PSS in water and hydrogels [5]. These insights could guide the design of advanced PEDOT:PSS biosensors for enhanced performance in biological environments.

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Multiscale simulations of the mechanism of a *de novo* designed Diels Alderase photoenzyme catalysing [2+2] cycloadditions: implications for photobiocatalyst design

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Photobiocatalysis is an emerging field where natural or artificial photoenzymes are used to drive chemical reactions, providing alternative, sustainable solar-driven solutions for various industrial reactions.[1,2] Photoenzymes use light to activate a light sensitive chromophore to trigger an enzymatic reaction providing routes to explore reactions that are thermally forbidden in the ground state. Recently, Green and coworkers have engineered a Diels Alderase photoenzyme that can catalyze a thermally forbidden [2+2] cycloaddition reaction.[3] Genetic code expansion was used to incorporate a triplet photosensitizer, benzophenone, into the protein scaffold of the Diels alderase enzyme that nominally catalyses [4+2] cycloadditions. Light absorption by the photosensitizer activates the substrate through triplet energy transfer, the rate of which was maximized using directed evolution. Here, we characterize the mechanism of this photobiocatalytic reaction using multiscale methods. We have used a combination of classical molecular dynamics and QM/MM methods to study the mechanism of product formation upon activation of the substrate. Two pathways of product formation in the enzyme namely, “Straight” and “Crossed” were explored. Our calculations reveal that the protein environment plays an important role in tuning the distribution of products formed by the two pathways. QM/MM calculations are also characterizing the excited state dynamics of the photoenzyme. The results provide detailed insight into the fundamental mechanisms of the reactions and the effects of the protein. This has potential applications for design and development of photobiocatalysts. Incorporating QM/MM calculations into protein design pipelines promises precise control of electronic properties and may help in the creation of new artificial photoenzymes. Such design, informed and driven by multiscale simulations, could pave the way for solar-driven enzymes that sustainably target a range of critical transformations such as electricity production, N_2 fixation, H_2 production, or CO_2 capture.

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Silver Iodide in Water – A Machine Learned Interatomic Potential with Electrostatics

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Polar surfaces form an area of great interest in the scientific community due to their interesting catalytic properties and inherent instability without reconstruction or charge adsorption from solution. A classic example of this is silver iodide, where the polar AgI-0001 face is one of the earliest known inorganic ice nucleators. This is a challenging system to handle computationally – any model must be able to explain the polar catastrophe inherent to polar surfaces, while also accurately capturing the interactions between silver iodide and water. Here, we train versions of MACE on this system with and without electrostatics. Using the case of a polar AgI slab in vacuum, we explore how different methods capture the diverging energies of ever-increasing slab widths. Then, we apply these models to the AgI-0001 face in water to explore how different models and surfaces structure the AgI-water contact layer.

Surfactants exhibit complex phase behaviour, forming aggregates when in solution of varying sizes and shapes. This can lead to a dramatic increase in the pKa of those surfactants with weak acid head groups, an archetypical example of which is fatty acids. It has long been known that fatty acids have pKas far above that of a typical carboxylic acid, despite having very similar chemical structures. Here, we study the effect of aggregation on the pKa of oleic acid, a C-18 fatty acid using an implentation of constant pH molecular dynamics in GROMACS. We demonstrate the transferability of a simple reference state and in doing so, are able to accurately predict the increase in pKa from a single surfactant to an aggregate, agreeing with previous work. We then study the effect of adjusting the ionic strength by addition of salt (KCl) on the behaviour of the system, finding that this leads to a reduction in this pKa upshift, in agreement qualitatively, though not quantitatively, with simple Debye-Huckel theory. We show the former arises due to the electrostatic interactions between the head groups of the oleic acid in larger aggregates, which are screened when the KCl is added to the solutions due to clustering of K+ ions at the interface, which leads to a reduction in the overall electrostatic potential. Our results highlight the non-ideality of the surfactant solutions and will help in predicting the impact that the solution's ionic strength has on the phase diagram of ionic surfactants.

Talk Abstract For CCPBioSim - Discovering Blood Brain Barrier Permeable Compounds with Cliques Descriptors

The blood-brain barrier (BBB) selectively regulates the passage of chemical compounds into and out of the central nervous system (CNS). As such, understanding the permeability of drug molecules through the BBB is key to treating neurological diseases and evaluating the response of the CNS to medical treatments. Within the last two decades, a diverse portfolio of machine learning (ML) models have been regularly utilized as a tool to predict, and, to a much lesser extent, understand, several functional properties of medicinal drugs, including their propensity to pass through the BBB. However, the most numerically accurate models to date lack transparency, as they typically rely on complex blends of different descriptors (or features or fingerprints), many of which are not necessarily interpretable in a straightforward fashion. In fact, the "black-box" nature of these models has prevented us from pinpointing any specific design rule to craft the next generation of pharmaceuticals that need to pass (or not) through the BBB. In this work, we have developed a ML model that leverages an uncomplicated, transparent set of descriptors to predict the permeability of drug molecules through the BBB. In addition to its simplicity, our model achieves comparable results in terms of accuracy compared to state-of-the-art models. As our method is transparent and requires very low computational resources, we demonstrate its capacity for large scale screening of chemical compounds by applying it to the entirety of Pubchem (approximately 110 million molecules). We use our method to identify previously unexplored compounds likely to be BBB permeable. We validate these predictions via metadynamics simulations.

Microtubule dynamics are defined by conformations and stability of clustered protofilaments

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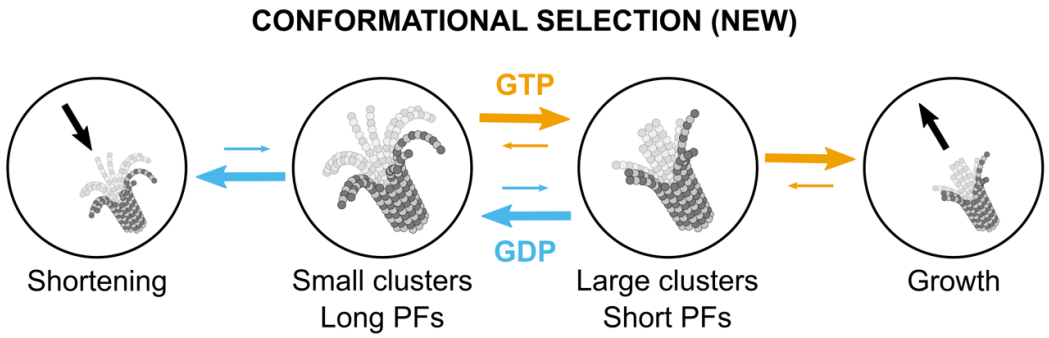

Microtubules are dynamic cytoskeletal polymers that add and lose tubulin dimers at their ends. Microtubule growth, shortening and transitions between them are linked to GTP hydrolysis. Recent evidence suggests that flexible tubulin protofilaments at microtubule ends adopt a variety of shapes, complicating structural analysis using conventional techniques. Therefore, the link between GTP hydrolysis, protofilament structure and microtubule polymerization state is poorly understood. Here, we investigate the conformational dynamics of microtubule ends using coarse-grained modelling supported by atomistic simulations and cryo-electron tomography [1]. We show that individual bent protofilaments organize in clusters, transient precursors to a straight microtubule lattice, with GTP-bound ends showing elevated and more persistent cluster formation. Differences in the mechanical properties of GTP- and GDP-protofilaments result in differences in intra-cluster tension, determining both clustering propensity and protofilament length. We propose that conformational selection at microtubule ends favours long-lived clusters of short GTP-protofilaments that are more prone to form a straight microtubule lattice and accommodate new tubulin dimers. Conversely, microtubule ends trapped in states with unevenly long and stiff GDP-protofilaments are more prone to shortening. We conclude that protofilament clustering is the key phenomenon that links the hydrolysis state of single tubulins to the polymerization state of the entire microtubule.

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Negative Chemotaxis of polymeric vesicles against lactic acid concentration gradient

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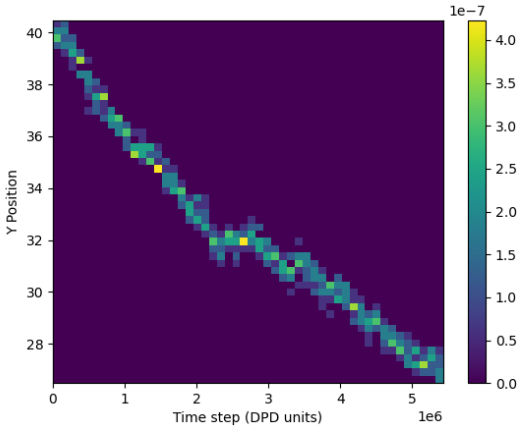
Negative chemotaxis is the ability of organisms or particles to move away from chemicals [1]. This can be triggered by binding of ligands or by external factors. Here, we use multi-scale methods to show how a PEG-b-PLA polymersome can exhibit negative chemotaxis in a lactic acid concentration gradient.

Initial atomistic simulations show that PEG-b-PLA copolymer chains in water lengthen when lactic acid is introduced. The atomistic simulations are then used to parametrise a Dissipative Particle Dynamics (DPD) model for copolymer chains. DPD is a coarse-grained simulation method in which large systems can be simulated using soft 'beads' representing groups of atoms. Here, we take advantage of the system size capability of DPD to simulate PEG-b-PLA polymer vesicles and the bilayers. For bilayers, we show that lactic acid binding to the inner hydrophobic PLA chains exposes them to surrounding water,and thereby increases the interfacial tension at the bilayer (membrane)-water interface. By the same mechanism, an interfacial tension gradient is produced along the polymer vesicles, triggering them to move away from the higher concentration of lactic acid.

Finally, we demonstrate how the rise in the membrane-water interfacial tension causes the polymeric vesicles to self-propel in response to an external gradient of lactic acid, allowing them to move from higher to lower concentration.



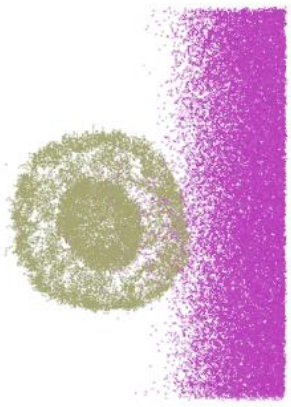


Figure: movement of a PEG-b-PLA polysome away from a high concentration of lactic acid.

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Machine learning potentials for accurate and efficient multiscale enzymatic Diels – Alder reaction modelling.

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To perform efficient computational screening of reactions catalysed by enzymes, an efficient multiscale potential needs to be selected. Usually, this involves a trade-off between accuracy and efficiency: either substantial sampling with semi-empirical methods or limited sampling with more accurate DFT are applied in QM/MM. Here, we propose the use of machine learning potentials[1] applied together with electrostatic machine learning embedding (EMLE)[2] as an alternative to the traditional QM/MM calculations. This ML(EMLE)/MM approach has already been proven to reduce the computational cost to below the level of semi-empirical QM/MM, and reproduce DFT-level QM/MM free energy profiles.[2]

AbyU is a powerful Diels-Alderase, which has been proven to be highly stable and mutable,[3,4] and can act on multiple substrates. Semi-empirical QM methods DFTB2, PM6 and AM1 were firstly applied in QM/MM, because they combine low computational cost with acceptable precision. For the same reaction, benchmarking using ML(EMLE)/MM indicated nanoseconds of simulations per day could be performed with the accuracy in energy and structures at the DFT-level. The EMLE approach is required to accurately capture the influence of the enzyme electric field on the reaction.

Present research is focused on applying ML(EMLE)/MM to non-natural Diels-Alder reactions catalysed by AbyU with substrates previously synthesised and tested by our experimental partners. The ultimate goal is to test this workflow with wide range of enzyme variants and demonstrate the potential of ML(EMLE)/MM approach for efficient screening of enzyme variants.

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Understanding protein interfacial interactions is crucial for applications in biotechnology and pharmaceuticals. In this study, we employ the Martini 3 coarse-grained force field to investigate the adsorption behavior of antibodies at water–hexadecane interfaces and their aggregation in both aqueous bulk and water–oil interfaces. Our simulations reveal that specific amino acids play a key role in adsorption, acting as interfacial "hot spots." These findings provide insights into the molecular mechanisms governing antibody behavior at interfaces, contributing to the rational design of protein-based formulations and biophysical studies.

Prediction of rhamnolipid partitioning into lipid bilayers using coarse-grained molecular dynamics with the Martini 3 force field

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Rhamnolipids (RLs) are bio-degradable, low-hazard biosurfactants, that can be extracted from cultures of *Pseudomonas* and other bacteria.[1] RLs can be used to adjust surface tension, as agents for environmental remediation, and as food/cosmetic additives.[2] Understanding uptake into biological systems is an important consideration which assessing the safety of chemicals. Our research focuses on prediction of the membrane-water partition coefficient (log K_{mw}) which has been shown to positively correlate with uptake in biological systems and can correctly capture the free energy profile of ionic surfactants.

We are developing coarse-grained (CG) models to represent RLs and predict log K_{mw} from the equilibrated ratio of concentration between membranes of 1-palmitoyl-2-oleoyl-glycero-3-phosphocholine (POPC) and aqueous solution. The CG models must capture the important interactions at the membrane-water interface, despite the loss of atomistic detail. Concentrations are calculated from the density distribution of RLs as a function of the coordinate perpendicular to the membrane, which is obtained by umbrella sampling. Our initial CG model of RLs was obtained from the automated CG mapping and parameterisation software cg_param, developed and maintained by our group.[3] We then developed this generic model using specialised knowledge from prior modelling studies dedicated to carbohydrates.[4] Given the lack of reference free energy profiles for RLs, we validate our model in several other ways: (1) we monitor the positioning of functional groups of RLs on the surface of the POPC membrane and angles between lipid tail groups and the membrane normal; (2) we test the transferability of models by reproducing physical properties; (3) we simulate the aggregation behaviour of RLs in brine with oil.

Our preliminary results show that the current cg_param provides sensible mapping and parameterisation for calculation of log K_{mw} for a typical RL, even without adjustment. Fine-tuning of CG RLs models according to guidelines set out for related molecules and moeities does not always lead to improved prediction of membrane-water partitioning and tends to overestimate hydrophobic interaction with the membrane. As well as accurately modelling membrane-water partitioning, we intend to use our optimised RL models to study the capture of oil droplets by RLs and to examine their effect on membrane curvature to gain better understanding of their interaction at the membrane surface.

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Controlling Polymorph Crystallisation Using Structured Ternary Fluids

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Structured ternary fluid (STF) mixtures consist of a small amphiphilic molecule, called a hydrotrope, that enhances the miscibility of two other immiscible components, typically oil and water. STFs, also called surfactant-free microemulsions or ultra-flexible microemulsions, have been shown to provide unprecedented control in the crystallisation of glycine polymorphs under ambient conditions.[1]

Typically, crystallisation of glycine happens under kinetic control, resulting in the formation of the metastable α-glycine polymorph. However, restricted diffusion of glycine within the hydroxyl network of an octanol/water/ethanol (OWE) mixture allows crystallisation to proceed via a higher nucleation rate and slower crystal growth pathway. The STF mixture acts as a nanocrystal incubator, prolonging locally high glycine supersaturations and allowing nanocrystals to exist for extended times.[1] This soft nanoconfinement means that crystallisation can occur under thermodynamic control, selectively producing slow-growing γ-glycine as the majority polymorph. Changing the STF composition and initial glycine supersaturation allows all three polymorphs to be targeted from the same OWE ternary mixture.

The enhanced control of glycine crystallisation within this STF system has been investigated further using atomistic molecular dynamics simulations (Fig. 1). The suitability of the glycine force field was assessed by calculating various solution and crystal-phase properties, such as lattice energy, hydration free energy, enthalpy of solution and polymorph free energy via the Einstein molecule method.[2] The degree of glycine nanoconfinement was evaluated for various STF compositions by calculation of diffusion coefficients and cluster lifetimes.

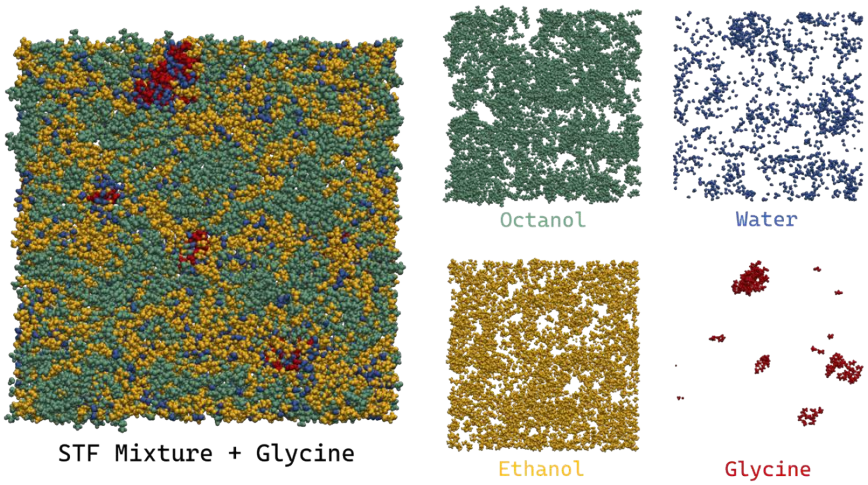

Figure 1: Glycine within a 50:10:40 wt% octanol/water/ethanol STF mixture (box length = 13.5 nm).

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Organic Thermoelectric Polymers: atomistic modelling of semicrystalline P3HT

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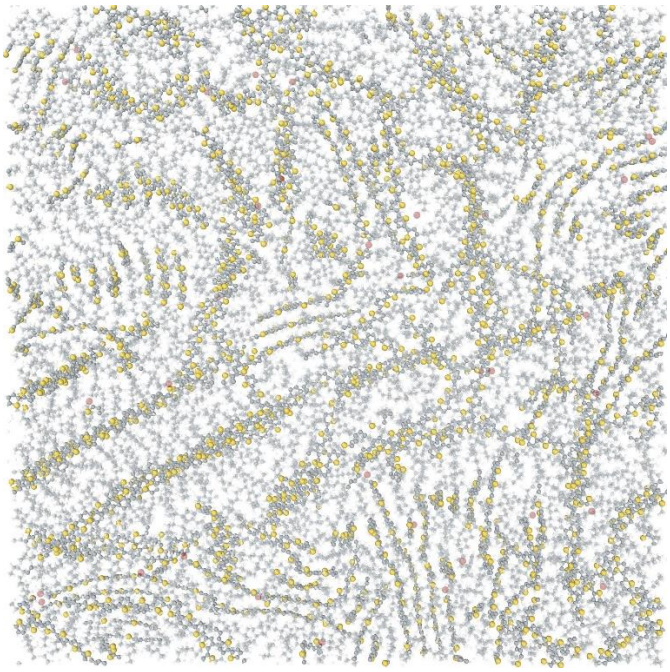
Organic Thermoelectric materials (OTE) show potential as a material for the production of green energy, through conversion of heat to electricity. Among OTE materials, polythiophenes are excellent candidates, although their structure-property relationships are to date poorly understood. Figuring out the structure-property relationships are particularly challenging for organic semiconducting polymers, because of their often complex semicrystalline structures and the big level of uncertainty regarding their detailed structure and composition. Computational modelling can shed new insights into the underlying causes of changes in properties, though the required scale and complexity make this quite challenging.

Here we will present a modelling study on poly(3-hexylthiophene) (P3HT) polymers, using molecular dynamics (MD) with GAFF2 forcefield, able to generate the complex semicrystalline structures of these polymers. We will compare results for both a 'dry' approach, where throughout the simulation the composition is unchanged, and a 'desolvation' approach, where at the start of the simulation the polymer is dissolved in solvent, which is stepwise removed until the desired composition is reached. Special focus will be on crystallinity, which we determine from local mass density and known to be a crucial parameter affecting the other parameters of interest (thermal conductivity, electrical conductivity and Seebeck coefficient). Thermal conductivity (determined using Muller-Plathe's rNEMD method), will also be briefly discussed.



Slice of a modelled P3HT structure (side-chains shown with transparency)

Enhancing Electrostatic Embedding for ML/MM Free Energy Simulations

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Machine learning potentials (MLPs) are becoming increasingly widespread due to their integration into existing methodologies and software. Many MLPs are trained to predict the intramolecular energetics of organic molecules, showing strong performance in this domain. To leverage these potentials in free energy calculations, MLPs have been incorporated into ML/MM simulations, where a small region of the system is modelled using MLPs, and the remainder is described with molecular mechanics (MM) force fields (FFs).

Most hybrid ML/MM simulations described to date employ mechanical embedding schemes, which rely on Lennard-Jones (LJ) and Coulomb terms to model intermolecular interactions. However, the performance of mechanical embedding ML/MM simulations remains a topic of ongoing discussion: while some studies report improved accuracy, others fail to demonstrate statistically significant improvements over well-parameterized FFs. A promising strategy to enhance the performance of

ML/MM simulations is to transition from mechanical embedding to electrostatic embedding, where polarisation effects on the ML region are explicitly incorporated. Recently developed electrostatic embedding methods, such as EMLE [1], have been designed specifically to account for these polarization effects.

In this poster, we present an absolute hydration free energy benchmark for a set of small organic molecules, demonstrating a robust methodology for training EMLE models and EMLE-compatible LJ parameters using quantum mechanical data. We also examine the accuracy limits associated with fitting to first principles and introduce an empirical adjustment to the model to improve alignment with experimental results. This methodology makes the simulations competitive with traditional MM FFs and enhances the applicability of electrostatic embedding ML/MM calculations for a set of druglike molecules where MM FFs fall short. Overall, our findings provide valuable insights into the current challenges and opportunities of electrostatic embedding ML/MM simulations, suggesting avenues for improving their accuracy.

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Understanding the Behaviour of Hole States for Copper Substitutionals in MgO

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Doped and undoped magnesium oxide has been of great interest for a long time, and still continues to be today. Whilst many transition metal ions have been investigated, studies of Cu^{2+} doping within bulk MgO are more sparse. The majority of research on Cu-doped MgO seems to largely be focused on either nanoparticles or uses in catalysis. Moreover, investigations on the bulk material have extensively probed the Jahn-Teller distortion induced by the substitutional, but not much else [1]. Our work focuses instead on the localisation and possible trapping of charge carriers within a $(CuO_6)^{10-}$ unit, as well as the processes of absorption and luminescence, transitioning to and from charged configurations. Whereas oxygen bound polarons have been observed with a number of doped metal oxides [2,3], currently, there is no evidence for the influence that copper has in MgO, in this regard. Equally, reports for transitions between charged states and the neutral system are limited, and thus through our investigations comparisons can be made between the doped and undoped materials. This work employs hybrid quantum mechanical (QM/MM) techniques to study a bulk MgO structure with a single doped copper ion at the centre, using the ChemShell code [4]. Initial calculations on the neutral doped structure are able to successfully replicate the previously reported Jahn-Teller distortion in the Cu-O bonds and further EPR investigations on this structure resemble experimental data closely. Through further probing of both the neutral and charged systems, it is clear that the Cu^{2+} is the preferential valence state in all cases and localisation of a hole species on a single oxygen ion is only possible under certain conditions, albeit such a configuration is not favourable.

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6th Manchester Multiscale Conference

Structural and dynamical assessment of the adsorption of silica oligomers on biomolecules via Molecular Dynamics

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Atom Probe Tomography (APT) has been recently proposed as an alternative procedure to determine three-dimensional structures of proteins [1]. APT consists of a spatially–resolved mass-spectrometry technique, whereby a biological specimen is first embedded by an amorphous silica matrix derived by orthosilicates like $Si(OH)_4$, and subsequently evaporated under irradiation of short laser pulses, upon application of a strong electric field to direct ejected ions towards a detecting surface. Building on APT, a funded EIC-Pathfinder consortium, named MIMOSA, aims to provide a new approach to determine protein structures, enabling high spatial resolution and chemical sensitivity by employing terahertz (THz) source lasers [2]. Notably, APT needs a bio compatible silica primer, keeping the native structural features of the system at hand while condensing into an amorphous, gel-like coating. Although promising, this APT-based procedure is still lacking a full understanding of its mechanism: our goal is to investigate both the adsorption of silica on biomolecule and their subsequent irradiation processes, employing the available computational techniques .

In this context, I will discuss a Molecular Dynamics (MD) protocol aimed at depicting the early stages of the embedding process, characterized by the presence of polymers of the matrix precursor $Si(OH)_4$ [3,4]. Specifically, the dynamical behavior of well-known proteins displaying different domain features (Ubiquitin, GFP, SUMO-1, Lysozyme T4) was monitored in a solution of water and oligomers of $Si(OH)_4$. Within the adsorption phase, we observe that the $Si(OH)_4$ oligomers have a negligible influence on the stable folded domains, although they affect the dynamics of disordered domains and flexible loops. These results are important in the context of APT applied to the characterization of intrinsically disordered proteins.

In addition, we are currently extending the complexity of this study, by introducing a multiscale treatment of the silica matrix via a coarse-grained reactive setup based on the MARTINI forcefield.

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Date: 28th January 2025

Capturing complexity in enzyme catalysis: Multidimensional Free Energy Landscape Explorations Using Multiscale Methods to Fight Infection Diseases.

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Understanding chemical reaction mechanisms can be a complex task, especially when enzymes are involved. Enzymes are highly specialized molecular systems that catalyse chemical reactions in a very specific way. These reactions often require multiple events to occur simultaneously for them to succeed. To better understand these reactions, a multiscale QM/MM approach is commonly employed to obtain the three-dimensional free energy surface of the process using methods as umbrella sampling.[1,2] This approach helps identify the minimal free energy path (MFEP) connecting the reactants and products regions. However, this method can be highly demanding in terms of computation, with resource requirements growing exponentially with the number of coordinates chosen to drive the simulations. This is known as the curse of dimensionality. In fact, if a reaction requires more than two coordinates to properly describe it, this method becomes inadequate. The adaptive string method is an alternative strategy to overcome this limitation because it can handle simultaneously many degrees of freedom to locate the MFEP and then define a one-dimensional reaction coordinate.[3,4] The present study uses this approach to explore chemical reactions involving up to 11 degrees of freedom or collective variables (CV) while using only a fraction of the computational power to find the MFEP on a free energy surface. This level of description is necessary to explain how enzymes like serine proteases and metallo-beta-lactamases inactivate antibiotics,[5] as well as how the main protease of coronavirus cleaves polypeptides necessary for replication of SARS-CoV-2.[6]

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Coarse-grained modeling of insulin adsorption on plasticized polyvinyl chloride surfaces

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During the infusion of drug, container-content interactions can lead to drug loss by sorption. Now, molecular simulation is more and more used in biomolecular systems to investigate drug/polymer interactions [1]. A previous study made the link between experimental and thermodynamic quantities during insulin monomer adsorption onto PE, PVC and PVC TOTM surfaces using all-atom force field [2]. These time-consuming simulations did not allow for a deep understanding of the plasticizer/protein and PVC/protein interactions. Here, Martini 3 model was used to model larger systems with one or several proteins on a surface. We modeled both insulin monomer and hexamer to study their interactions with a non-plasticized PVC surface, and two plasticized PVC surface with di(2-Ethylhexyl) terephtalate (DEHT) and tris(2-ethylhexyl) trimellitate (TOTM) plasticizers. Studying these systems with a coarse-grained model helped us have a better understanding of protein/surface interactions with the different components of the surface. We focused on the adsorption of several proteins on the surface to better characterize the thermodynamics of adsorption. Indeed, with coarse-grained simulations, it is possible to investigate the dependence of the potential of mean force on the starting configuration, which remains challenging to do with atomistic model.

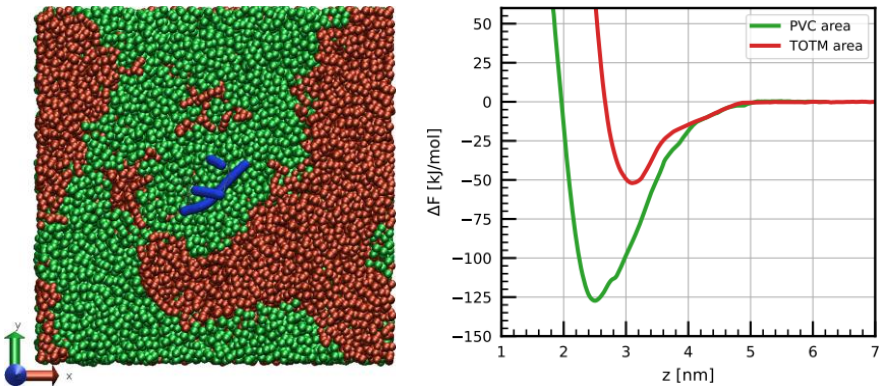

Figure 1 : System insulin monomer on PVC TOTM surface (PVC chains in green, TOTM in red), and potential of mean force depending on the sampled area (PVC or TOTM).

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Understanding electrochemical interfaces with neural functional theory

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In systems which make use of the electric double layer, understanding the link between structure on the molecular level and macroscopic properties is essential in maximising energy storage efficiency. However, the fact that the electric double layer is inherently microscopic in scale (< 50 nm), and that the use of porous carbon electrodes introduces nanoscale confinement, leads to these systems showing a strong dependence on atomic/molecular changes in both the electrolyte and electrode. While MD methods can be applied for a range of different electrolytes, the sensitivity of nanoconfined systems to the chosen particle density can lead to variability in results based on the chosen number of particles. cDFT avoids this by working within the grand canonical ensemble, allowing the density within the pore to be determined subject to a choice of chemical potential.

We make use of improved cDFT functionals based on neural networks[1,2], which can determine the static thermodynamics of these systems to a simulation level of accuracy, to develop a model of an electrode-electrolyte interface. This model makes use of cDFT to determine separately the behaviour of a model electrode and electrolyte, both treated as a different fluid, with an applied external potential to determine the “voltage”. While our example system makes use of relatively simple liquid models, the method is general and will be readily applicable to neural functionals of more complex fluids.

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Understanding DNA-Protein Interactions in Eukaryotic Topoisomerases through atomistic molecular simulations

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Topoisomerases are homeostatic enzymes, responsible for maintaining the delicate topological state of DNA. During the catalytic cycle of topoisomerase, DNA is passed through a transient break in a DNA-protein complex and out the enzyme [1]. The passage of the DNA through the internal cavity of topoisomerase and out of the exit gate performs the topological simplification. Topoisomerases are overexpressed in cancerous cells, making them a prime anti-cancer drug target. There are clinically approved topoisomerase inhibitors already utilised in cancer treatments [2, 3]. Humans express two isoforms of type IIA topoisomerase, however, current topoisomerase cancer drugs, such as etoposide, target human isoforms non-specifically [4]. Although both isoforms share 68% sequence homology, their *in vivo* functions remain distinct [5]. Understanding how structural differences between the two isoforms manifest in their functions is vital for selective cancer treatments.

We present a computational protocol based on atomistic molecular dynamics (MD) simulations, through which the complex DNA-protein interactions in the two topoisomerase isoforms can be better understood. We showcase results from MD simulations of the transfer (T) segment DNA inside the internal cavity with each human isoform at the exit gate. This region is the most variable region between the isoforms, hence, observed changes between the DNA-protein dynamics are integral to understanding experimental evidence. Using a mixture of conventional MD-analysis methods and unsupervised machine learning techniques, we elucidate how the internal DNA-protein interactions are essential for strand passage. From this, we identify regions of structural importance in the underexplored exit gate. By comparing the behaviours of eukaryotic topoisomerases isoforms *in silico*, we hope to explain observed known differences *in vitro*.

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Spectral tuning in a *de novo* riboflavin protein

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The field of *de novo* protein design has grown rapidly in recent years, with significant advances in available computational and experimental tools. *De novo* proteins offer great potential for designed applications in catalysis (including electrocatalysis and photocatalysis), biomolecular electronics, and engineering biology. The *de novo* "maquette" heme b binding protein 4D2, and its designed and evolved variants, provide an expandable, modular *de novo* protein platform for precision redox engineering.[1] A particular aim in their development is to incorporate photosensitizers, to allow for e.g. designed electron transfer.

4D2 has been redesigned to covalently bind a flavin chromophore to introduce photo-reactivity to the system. Our study is focussed on computing accurate spectroscopic properties of flavin-4D2 using QM/MM which can then be incorporated into protein design pipelines.

QM/MM dynamics simulations, based on snapshots from classical MD simulations of flavin-4D2, served as the basis for computation of the electronic absorption spectrum. The spectrum calculations were done using Linear-Response TD-DFT (ωb97x-D3, def2-svp). These calculations revealed that the major electronic transitions involved in the excitation are pi-pi* transitions from S_0 to S_1 and S_0 to S_4. We are currently studying the effect of protein environment on the absorption spectrum in flavin-4D2 to enable rational design of protein absorption. These calculations will serve as the first step in characterizing photoinduced electron transfer in de novo proteins while also shedding light on the "structure-spectrum" [3] problem paving the way for rational design and tuning of photoactive proteins for applications such as light harvesting, electron transfer or photocatalysis.[4]

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FibrilGen: a program to template cross-$\boldsymbol{\beta}$ nanostructures at the atomic level

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Rational design of cross-β nanofibrils for drug delivery and cell culture is challenging due to the high sensitivity of these self-assembled peptide structures to factors such as peptide sequence[1], solvent polarity[2], pH[3], and incubation time[4]. Due to their inhomogeneous nature, experimental characterisation of structure by techniques such as transmission electron microscopy and NMR can also be problematic.[5] To allow for systematic exploration of cross-β nanostructures by computational methods, therefore, we have developed a python library called FibrilGen, which enables top-down construction and visualisation in PyMOL of a range of cross-β fibril morphologies at the atomic level. The generated models enable comparison with structural data from NMR and electron microscopy, as well as inputs for molecular dynamics simulations. Here, we use our program to atomistically model rods and tubes consistent with cryo-EM morphologies, and then we analyse the thermodynamic stability of our generated structures using molecular dynamics simulations. We also analyse interactions stabilizing the cross-β conformations and relate them to fibril morphologies observed in regular transmission electron microscopy images. Based on the modelled systems, we conclude our program can generate cross-β structures comparable to experimental data, and can provide insight into templating and designing hypothetical cross-β nanostructures.

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Structure-based virtual screening targeting APSR: exploring covalent inhibitors against *Pseudomonas aeruginosa*

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The increasing prevalence of antibiotic-resistant Pseudomonas aeruginosa demands the urgent need for novel therapeutic strategies. In this context, adenosine phosphosulphate reductase (APSR) represents a promising target due to its role in reducing inorganic sulphate to sulphite - a critical step in the biosynthesis of sulfur-containing biomolecules. The enzyme's activity is mediated by the catalytic cysteine (Cys256) located in the flexible C-terminal tail that is unresolved from the crystallographic structure. To address this limitation, we used AlphaFold2[1] to build the C-terminal tail, paving the basis for our discovery campaign of covalent inhibitors. From the modelled APSR structure in complex with its natural substrate, adenosine phosphosulphate (APS), we developed a virtual screening workflow to discover covalent compounds targeting Cys256. By substituting the phosphosulphate group with four reactive warheads (acrylamide, chloroacetamide, cyanoacrylamide and vinyl sulfone), four Michaelis complexes were designed to react with Cys256. These complexes were refined through QM/MM minimization and the resulting optimized geometries of the four Michaelis complexes were used as a basis to design the pharmacophore model, allowing the retention of potential covalent inhibitors to react with the catalytic cysteine and simulate the substrate interactions. Enamine covalent libraries were screened against the pharmacophore model and compounds meeting the geometric criteria were refined using Glide CovDock (Schrodinger, Inc.). The covalent-bound ligand was eventually rescored via Binding Pose Metadynamics to assess the binding mode and interaction stability [2]. Among nine compounds selected via our virtual screening workflow, enzymatic assays revealed that two compounds containing a vinyl-sulphone and chloroacetamide warhead each inhibited APSR activity. In particular, the vinyl-sulphone compound decreased *P. aeruginosa* by 20-30% in cellular assays. These results provide evidence that targeting the catalytic cysteine of APSR can disrupt sulfur biosynthesis and impair bacterial proliferation. Quantum Mechanics/Molecular Mechanics (QM/MM) simulations investigating the APSR catalytic mechanism is currently underway and suggest that the $[4Fe\text{-}4S(Cys\text{-}S)4]^{2-}$ cluster is involved in active site pre-organizing and facilitates substrate binding. It orients Lys-144 to optimize APS interaction, while Lys-144 establishes a critical link between APS and the coordinating Cys-140. Consequently, the activated sulphate group is susceptible to nucleophilic attack by the catalytic Cys-256, which forms a covalent S-sulphocysteine intermediate that is subsequently released by thioredoxin, ultimately resulting in the release of sulphite. [3]

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Transforming Tuberculosis Care: Rapid Accurate and Reliable Computer-Based Prediction of Drug Resistance to Guide Targeted Treatments

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Abstract

As one of the deadliest infectious diseases in the world, tuberculosis (TB) is responsible for millions of new cases and deaths reported annually. The rise of drug-resistant TB, particularly resistance to first-line treatments like rifampicin (RIF), presents a critical challenge for global health, which complicates the treatment strategies and calls for effective diagnostic and predictive tools. In this study, we introduce an ensemble-based molecular dynamics computer simulation method – TIES_PM – to predict RIF resistance in RNA polymerase. Via calculations of 61 mutations, including those in the rifampicin resistance-determining region, TIES_PM produces stable and reliable results with small error margins, as well as good agreement with clinical data. The quality and consistency of clinical data is of critical importance to validate the computational predictions. In addition, the method's flexibility offers potential for extending predictions to other first-line drugs and drug-resistant diseases. This adaptability positions it as a valuable complement to existing diagnostic tools, providing a cost-effective and accurate method for drug resistance screening in both research and clinical areas.

Applicability of the Thermodynamic and Mechanical Route to the Young Equation for Rigid and Soft Solids: A Molecular Dynamics Simulations Study of a Lennard-Jones System Model

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The wetting properties of a liquid in contact with a solid are commonly described by the Young's equation, which defines the relationship between the angle made by a fluid droplet onto the solid surface and the interfacial properties of the different interfaces involved. When modelling such interfacial systems several assumptions are usually made to determine this angle of contact, such as a completely frozen solid or the use of the tension at the interface instead of the surface free energy. In this work, we perform Molecular Dynamics simulations of a Lennard-Jones liquid in contact with a Lennard-Jones crystal and compare the contact angles measured from a droplet simulation with those calculated using the Young's equation with both the surface free energy and the surface stress. We analyse cases where the solid atoms are kept frozen in their positions and where they are allowed to relax and simulate surfaces with different wettability and degree of softness. Our results show that using either surface free energy or surface stress in the Young's equation leads to similar contact angles but different interfacial properties. We find that the approximation of keeping the solid atoms frozen must be done with care especially if the liquid can efficiently pack at the interface. Finally, we show that, to correctly reproduce the measured contact angles, the quantity to be used in the Young's equation is the surface free energy only and that the error committed in using the surface stress becomes larger as the softness of the solid increases.

Characterizing graphene biointeractions: coarse-grained modeling of ion binding, small molecule adsorption and protein corona formation

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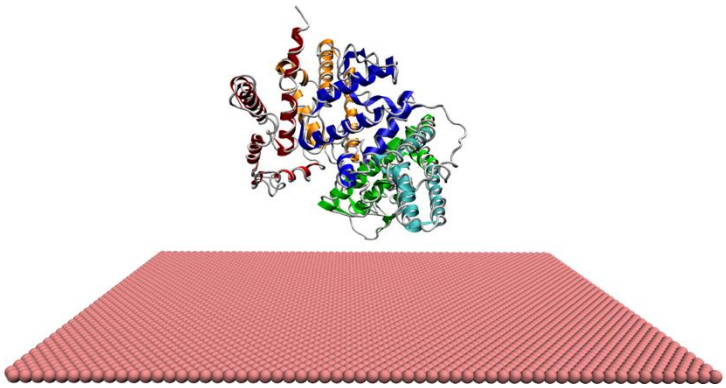
The increasing use of graphene in nanomedicine demands a deeper understanding of its interactions with biomolecules at the molecular level. In this study, we use coarse-grained (CG) modeling to investigate the behavior of graphene flakes in biological environments, i.e. when interacting with ions, small molecules and serum proteins, among which human serum albumin (HSA) is chosen as case study. Our work is based on the coarse-grained model of graphene developed by some of us [1], which is compatible with the version 3 of the MARTINI force field (FF). We perform CG molecular dynamics (MD) simulations of a graphene sheet immersed in a realistic physiological environment and compare our results with available experimental or all-atom (AA) MD data. Finally, by CG simulations we aim at characterizing protein corona formation on graphene surface, analyzing HSA adsorption. We believe that this work will provide a comprehensive computational framework for understanding graphene-biomolecule interactions, offering valuable insights into its potential for biomedical applications.



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Protocols for free energy predictions for beta-lactamases: insights from cross-class inhibitors

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While relative binding free energy (RBFE) methods are widely used for many pharmaceutically relevant protein targets, challenges remain. For example, open-source tools do not support the easy setup and simulation of metalloproteins, especially when small molecules directly coordinate to the metal site. Here, we introduce meze, an open-source, metalloenzyme-parameterization program for setting up molecular dynamics (MD) simulations and RBFE calculations of metalloproteins. We use meze to parameterize two nonbonded metal parameter setups for VIM-2, a metallo-β-lactamase (MBL), with two active site zinc ions. We also evaluate the performance of RBFE methods for KPC-2, a serine-β-lactamase (SBL), and the two metal models for VIM-2, set up by meze [1], using a set of phosphonate-based inhibitors with known cross-class affinity for SBLs and MBLs [2]. The first metal model is a restraint-based approach, which combines FF14SB zinc parameters with harmonic restraints between the zincs and their coordinating residues. The second approach uses an upgraded Amber force field (UAFF) for zinc-metalloproteins with adjusted partial charges and nonbonded terms for zinc-coordinating residues [3, 4]. The KPC-2 binding free energy estimates are within expected literature accuracies for the inhibitor series with a mean absolute error of 0.45 kcal/mol and a Pearson's correlation coefficient of 0.93. For VIM-2, the UAFF approach has improved correlation from 0.55 to 0.78, compared to the restraint approach. The presented strategies highlight that simple metal parameter models can provide predictive free energy estimates but leave room for improvement in their modeling of coordination sites and, as a result, their accuracy. The meze program aims to improve the ease of metalloprotein parameterization by only requiring simple inputs from the user and providing inputs needed for RBFE or MD workflows. The modular program, compatible with Amber and BioSimSpace [5], offers a few existing parameter options with improved modeling options under development.

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