5th CCPBioSim/CCP5 Multiscale Modelling Conference

Programme

Day 1 - Monday 3rd April 2023

12:00 – 13:20	**Registration and Lunch**
13:20 – 13:30	Welcome / Introduction
13:30 – 14:05	Rosana Collepardo *Title*
14:05 – 14:25	Daniel Del Hoyo *Scipion-chem: an Open Platform for Virtual Drug Screening*
14:25 – 14:45	Mark Driver *Protein-RNA Condensates: Complementary or Competing Interactions in ALS Progression?*
14:45 – 15:15	**Coffee Break**
15:15 – 15:50	Modesto Orozco *Advances and challenges in the simulation of DNA*
15:50 – 16:10	Giulia Frigerio *Molecular Dynamics Simulations of cRGD-conjugated PEGylated TiO2 Nanoparticles for Targeted Photodynamic Therapy*
16:10 – 17:00	*Flash Talks A – Odd Poster Numbers*
17:00 – 18:30	**Poster Session A**

Day 2 - Tuesday 4th April 2023

08:30 – 09:00	**Welcome**
09:00 – 09:35	Björn Baumeier *Theoretical Spectroscopy of Complex Multiscale Materials with Embedded Green's Function Methods*
09:35 – 09:55	Lianne Gahan *Coarse Grained Modelling of Amyloid Fibril Formation, Inhibition and Disruption Towards Alzheimer's Drug Design*
09:55 – 10:15	Marko Hanzevacki *Multiscale Modelling of Reactions in Radical Metalloenzymes*
10:15 – 10:35	Rachel Hendrikse *Using Many-body Dissipative Particle Dynamics to Predict the Surface Tension of Pure and Mixed Systems*
10:35 – 11:05	**Coffee Break**
11:05 – 11:40	Paola Carbone *Modelling the structure of the carbon/electrolyte interface using QM/MD simulations and machine learning*

11:40 – 12:00	Victoria Hill *DNA Damage Competes With Sequence to Pin a Plectoneme*
12:00 – 13:30	**Lunch Break**
13:30 – 14:05	Halim Kusumaatmaja *Wetting of Biomolecular Condensates in Biological Cells*
14:05 – 14:25	Jaehyeok Jin *Systematic Design Principles for Combining Rules in Bottom-up Coarse-Grained Interactions*
14:25 – 14:45	James Krieger *Scipion-EM-ProDy: A Graphical Interface for the ProDy Python Package enabling Integration of Databases, Simulations and Cryo-Electron Microscopy Image Processing*
14:45 – 15:15	**Coffee Break**
15:15 – 15:50	Laura Orellana *Connecting Biological Scales – From Disease Mutations to Protein Mechanisms Through Coarse-grained and Atomistic Simulations*
15:50 – 16:10	Tomas Kubar *Simulation of Reactions in Biomolecular Complexes: Blending the Flavours*
16:10 – 17:00	*Flash Talks B – Even Poster Numbers*
17:00 – 18:30	**Poster Session B**
19:00	**Conference Dinner**

Day 3 - Wednesday 5th April 2023

08:30 – 09:00	**Welcome**
09:00 – 09:35	Cecilia Clementi *Title*
09:35 – 09:55	Andrea Levy *Free Energy Profiles of Transition Metal Drug Binding From Multilevel Thermodynamic Integration*
09:55 – 10:15	Antoni Salom Català *Computational Modelling of Gas-Liquid Pickering Interfacial Catalysts Using Dissipative Particle Dynamics*
10:15 – 10:35	Sergio Sousa *Application of QM/MM Methods to Understand the Role Played by Different Amino Acid Residues in the Catalytic Mechanism of Plastic PET degrading Enzymes*
10:35 – 11:05	**Coffee Break**
11:05 – 11:25	Tseden Taddese *Mesoscale Modelling and Simulation of Water/poly(ethylene oxide) on Silica Surfaces*
11:25 – 11:45	Stephen Yeandel *Interfacial Free Energies from MD Simulations: Application to CaSO4.xH2O*

11:45 – 12:20	Matteo Salvalaglio *Nucleation of Biomolecular Condensates from Simulations and Experiments in Finite-Size Volumes*
12:20 – 14:00	**Lunch and Close**

Posters

Number	Presenter	Title
1	Ahmed, Saleh Hussein Abduraboh	Structural Properties and Insights of Water-methanol Mixtures – An Atomistic Molecular Dynamics Simulations Study
2	Boeser, Julian	Reduction Pathway of Glutaredoxin 1 Investigated with QM/MM Molecular Dynamics Using a Neural Network Correction
3	Chao, Kin	A Multiscale Simulation Approach to Characterise the Glidesome-associated Connector (GAC) from Toxoplasma gondii
4	Chen, Zhongquan	Multiscale Modelling of Charge Dynamics in Neuromorphic Devices
5	Chergui, Yahia	Measurement of ZnO Atomic Distances under Isothermal and Isobaric Ensembles: A Molecular Dynamics Prediction
6	Eichinger, Lena	Exploring the Mechanism of Autophosphorylation in the Bacterial Sensory System using QM/MM Simulations
7	El-Sayed, Sherihan	Insights into NLRP3 Inflammasome Activation Using MD Simulation
8	Fan, Lanyu	Study of Monoclonal Antibody Formulations to Decrease Aggregation Using Molecular Simulations
9	Farouq, Haider	Adsorption of The Spike Protein On a Model Silica Surface
10	Ferguson, George	Investigating the Intercalation of Cryptolepine between DNA Watson and Crick Base Pairs
11	Gonçalves de Abrantes, Juliana	Quantum Tunnelling in Methylated DNA
12	Güven, Jasmin	Potential Inhibitors for Beta-lactamases Under the Alchemical Microscope
13	Hoffmann, David	Exciton Transfer Simulations in Light Harvesting Complexes Accelerated by Machine Learning
14	Hori, Naoto	Mg2+-induced Folding and Misfolding of Ribozyme Studied by

		Coarse-grained RNA Model
15	Huertas, Jan	The Pioneer Transcription Factor Oct4 Alters Chromatin Packing
16	Iorio, Antonio	Multiscale Shear Flow Induced Aggregation of Aβ Amyloid in Interstitial Brain Space
17	Kanagarajan, Ajeeth	Studying the Permeation of Small Molecules in Poly Vinyl Acetate, PVAc
18	Laborie, Emeline	Towards a Realistic Multiscale Model of Cilia Driven Clearance
19	Lightfoot, Jasmine	Understanding the Improved Separation Performance of Asymmetric Polymer Composite Membranes
20	Maristany, Maria Julia	Mechanistic Properties of DNA Govern Nucleosome Unwrapping
21	Morbec, Juliana	Pentacene Molecules Meet Transition Metal Dichalcogenides for Photovoltaic Energy Harvesting
22	Musleh, Sondos	Absolute Binding Free Energy Calculations of Monosaccharide and Oligosaccharide Ligands of Concanavalin A
23	Nesabi, Azam	Predicting the Aggregation of Small Molecules by Molecular Dynamics Simulation
24	Ngambia, Audrey	Molecular Models of Realistic Biochars with Controlled Porosity
25	Robins, James	Development of Coarse-grained Molecular Simulation Model for Polymer-RNA Nanoparticles
26	Slocombe, Louie	Quantum Tunnelling Effects in the Guanine-Thymine Wobble Misincorporation via Tautomerism
27	Spies, Katharina	CP-DFTB/MM Simulations of Tyrosine-tyrosine PCET in RNR-Inspired Model Systems
28	Stavert, Tom	Modelling-Assisted Development of Green Routes to Ordered Mesoporous Silica
29	Stennett, Amelia	Turning up the Heat: Understanding of the Sensitivity of NLRP3 Inflammasome to Elevated Temperature
30	Trnka, Tomáš	Efficient Pipe Interface Between the Amsterdam Modeling Suite and External Software
31	Vallee, Cedric	Investigation of Heavy Water Effect on Ion Selectivity in ASIC1
32	van Vuren, Oscar	Developing Standardised Modelling Workflows for Multiscale QM/MM Studies of Metal Oxides

33	Vu, Huong	Plus and Minus Ends of Microtubules Respond Asymmetrically to Kinesin Binding by a Long-range Directionally Driven Allosteric Mechanism
34	Walsworth, Sam	Cytotoxic Ag-NHC Complexes as LDHA Inhibitors
35	Wang, Yuhan	Using Molecular Dynamics Simulation to Predict the Aggregation Propensity of Monoclonal Antibodies Formulations & Accelerate Development
36	Winokan, Max	The Replisome Environment and DNA Point Mutations: Multiscale Simulations of G-C Tautomerism and PcrA Helicase
37	Xu, Shangze	Mechanistic Investigation of the Androgen Receptor DNA-Binding Domain and Modulation via Direct Interactions with DNA Abasic Sites: Understanding the Mechanisms Involved in Castration-Resistant Prostate Cancer
38	Zaki, Afroditi Maria	Binding and Mode of Action of the Ectoparasite Fluralaner to the GABA RDL Receptor of Insects

Scipion-chem: an open platform for Virtual Drug Screening

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Virtual Drug Screening (VDS) tackles the problem of Drug Discovery by computationally reducing the number of potential pharmacological molecules which need to be tested experimentally in order to find a new drug. To do so, several approaches have been developed through the years, typically focusing either on the receptor structure and its physicochemical characteristics (Structure Based Virtual Screening) or in those of the potential ligands (Ligand Based Virtual Screening).

Scipion is a workflow engine [1] particularly well-suited for structural studies of biological macromolecules. As for today, it includes resources for the structure determination by single-particle analysis in CryoEM and atomic model building. Here, we present Scipion-chem, a new branch oriented to VDS. A total of 10 plugins have already been integrated, and they enable the user to acces to some of the most common programs used in the field (Shcrödinger[2] and AutoDock[3] among others). All these programs can be used through the Scipion Graphic User Interface (GUI) to execute and analyze typical VDS tasks such as protein and ligand preparation, definition of structural Regions Of Interest (ROIs), docking (either on the whole structure or on the defined ROIs) and molecular dynamics. In addition, from the Scipion team we have developed several consensus protocols, which combine results from the different integrated programs in order to generate more robusts predictions. On the backstage, Scipion also facilitates the interoperatibility of those different software, by handling the different file format conversions needed for the correct functioning of the workflow, while tracking all the intermediate files, parameters and user decisions.

In summary, in this communication we present Scipion-chem, an accesible, interoperable and traceable platform which provides the user all the tools needed for carrying out a succesful VDS workflow. Scipion-chem is openly available at https://github.com/scipion-chem

References

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PROTEIN-RNA CONDENSATES: COMPLEMENTARY OR COMPETING INTERACTIONS IN ALS PROGRESSION?

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Membraneless organelles within cells provide organisation of the intracellular environment through the process of liquid liquid phase separation (LLPS). The Fused in Sarcoma (FUS) protein is an RNA binding protein that undergoes LLPS with RNA as part of normal activity in healthy cells. PolyPR and polyGR, dipeptide repeat proteins (DPRs) caused by C9orf72 repeat expansion disorders, have been shown to promote protein aggregation of RNA binding proteins, including FUS. This aggregation contributes to the progression of the neurodegenerative diseases ALS (amyotrophic lateral sclerosis) and FTD (frontotemporal dementia), which have ineffective treatments and no cure. The pathway towards protein aggregation, and away from stable condensates, is poorly understood, but has been linked to changes in condensate behaviour induced by the addition of DPRs. Here we investigate the effect of DPR and RNA on the stability of FUS condensates through molecular dynamics simulations.

Condensate formation is driven by electrostatic (RNA-FUS and RNA-DPR), cation-pi (FUS-DPR and FUS-FUS) and hydrophobic (FUS-FUS) interactions between molecules. To study the competition between these molecular interactions, we use our previously developed coarse-grained molecular dynamics (CGMD) models that enable the simulation of large collections of biomolecules at thermodynamic equilibrium to study essential cellular processes. A ternary phase diagram will be used to present the results of simulations on FUS-DPR-RNA mixtures using a 1 bead-per-amino-acid (1BPA) [1-3] and a 3 bead-per-nucleotide (3BPN) [4] model. Molecular contact maps and radial density profiles were used to categorise topological changes inside the condensates across the phase diagram. A DPR length dependence was observed to influence transition between distinct topological regimes. We anticipate these insights to shed light on the toxic effect of arginine-containing DPRs and potentially contribute to the disclosure of new therapeutic avenues.

References

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Advances and challenges in the simulation of DNA

Modesto Orozco

DNA is a one pf the most remarkable examples of a multi-scale multi-physics problem. Individual interactions occur in the sub-nanometer scale (the nucleobase), while global effects involve the entire chromatin fiber, which for humans measures 2 meters for each cell. Interactions affecting the DNA happens in the femto to pico-second time scale, but impact the biology of DNA in the hours to years time scale. DNA represents then a major challenge for simulation techniques that needs to tackle this multi-scale problem by using a variety of approaches. I will summarize in my talk our efforts to develop a continuum of methodologies able to capture DNA properties from the small (electron) to the large (chromosome) scales

Molecular dynamics simulations of cRGD-conjugated PEGylated TiO_2 nanoparticles for targeted photodynamic therapy

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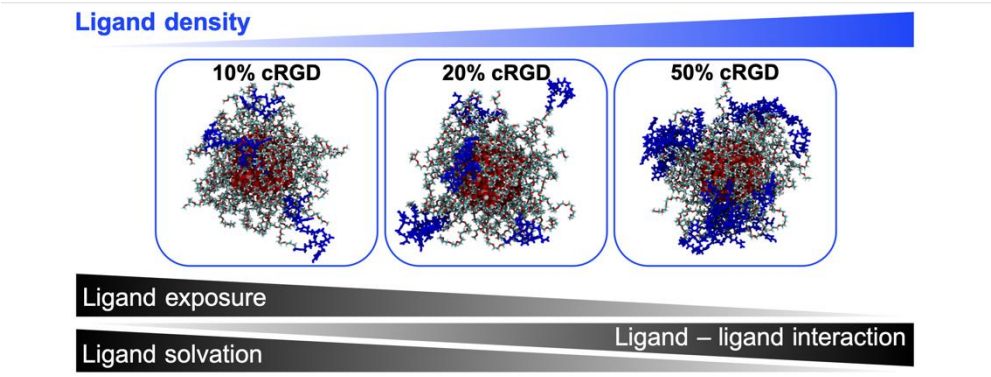
Active targeting strategies, exploiting the biological interaction between ligands on the surface of nanoparticles and the cell targets, are known to increase the therapeutic efficacy of cancer treatments with respect to passive targeting strategies that are mainly based on the enhanced permeability and retention effect of tumor cells [1]. Thus, the conjugation of nanoparticles with cyclic RGD (cRGD) peptides affine to $\alpha_V\beta_3$ integrins is a promising approach in nanomedicine to efficiently reduce off-targeting effects and enhance the cellular uptake by integrin-overexpressing tumour cells [2].
We used atomistic molecular dynamics simulations to evaluate key structural-functional parameters of cRGD-conjugated TiO_2 nanoparticles [3] for an effective binding activity towards $\alpha_V\beta_3$ integrins. An increasing number of cRGD ligands has been conjugated to PEG chains, grafted to highly curved TiO_2 nanoparticles, to unveil the impact of cRGD density on its presentation, diffusion, and conformation in an explicit aqueous environment. Our findings strongly suggest that the ligand density modulation is a key factor in the design of cRGD-targeting nanodevices to maximize their binding efficiency to over-expressed $\alpha_V\beta_3$ integrins [4].



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Invited Talk

Theoretical Spectroscopy of Complex Multiscale Materials with Embedded Green's Function Methods

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Understanding and controlling electronically excited states and their fundamental processes is crucial for the design of custom materials for, e.g., solar energy conversion and storage, light emission, quantum information, and sensing applications. First principles calculations, or theoretical spectroscopy, play a front role in this effort because they allow for an atomistic understanding of the formation, transport, and dissociation of excited states. However, materials that support such processes are often characterized by complex supramolecular structures. In these structures, excited state processes can span wide length- and timescales, from molecular building blocks to macromolecular assemblies, and from sub-picosecond exciton generation to transport processes on nanosecond timescales.

In this talk we will give an overview about how we tackle (a part of) this challenge of complexity with quantum-quantum and quantum-classical embedding methods employing many-body Green's functions (*GW*-BSE) for probing quasi-particle and electron-hole type excitations [1,2].

As a prototypical application, we will first consider the determination of position-resolved ionization and exciton (binding) energies in disordered molecular thin films for OLED applications, as well as the prediction of their direct/inverse photoemission [3] and optical spectra. The obtained results allow, for instance, to make a link between surface sensitive spectroscopy and bulk electronic structure, relevant for electronic device simulation and optimization. Further examples will cover studies of the solvent-sensitivity of charge-transfer state formation in lipophilic dyes [4], and conversion dynamics between localized and charge-transfer excitons in donor-acceptor materials.

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Coarse grained modelling of amyloid fibril formation, inhibition and disruption towards Alzheimer's drug design

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Amyloid Proteins and their hallmark fibrous structures are central to many disease pathologies such as Alzheimer's[1], Type 2 Diabetes and Parkinson's[2]. Many proteins are capable of forming amyloid fibres, and above a critical concentration, the fibrillar structure is the most energetically stable structure that amyloid proteins can form. We use an in-house dynamic Monte Carlo simulation scheme[3,4] in the NVT ensemble to model amyloid fibre assembly and its inhibition. In the context of this work, we represent amyloid protein monomers with a single rod-shaped particle. These protein monomers are modelled as spherocylinders interacting via attractive patches and a volume excluding potential. We model inhibitors as isotropically interacting spheres that are not self-interacting but interact with the spherocylinders via a similar potential, requiring the attractive patch to point towards the sphere.

We have identified several regions of parameter space where significant fibril inhibition occurs[5]. By varying properties such as inhibitor radius, inhibitor-protein interaction strength, protein aspect ratio and relative protein population, we observe mechanisms such as fibril capping, monomer and small cluster binding and surface coverage of clusters. We have observed key relationships between rod aspect ratio and the level of structural order in large clusters. Large inhibitory molecules can disrupt this order in almost all conditions considered. We have found that inhibitors can both aid and prevent fibrillisation in different regions of parameter space by modifying the strength of the interaction between the protein monomer and inhibitory particles. These mechanisms have implications for drug design to prevent further fibril growth. In preventing fibril growth, we could prevent the production of neurotoxic complexes in the following cases: (a) in an excess of free monomers by disrupting fibril assembly as it occurs, potentially preventing further brain degradation caused by downstream effects of additional fibrillisation. And (b) by disrupting and disaggregating existing fibril populations in a diseased brain, providing an opportunity for clearance of smaller, less ordered structures.

References

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Multiscale Modelling of Reactions in Radical Metalloenzymes

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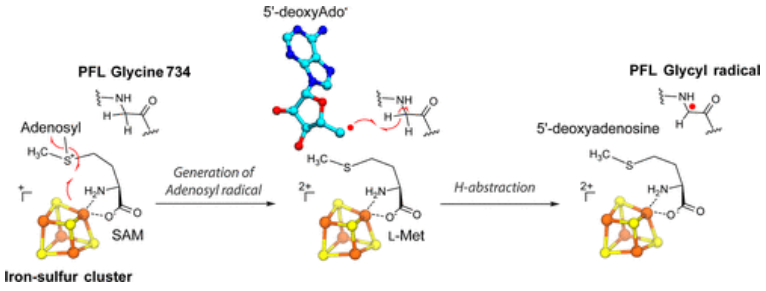
QM/MM calculations can identify enzyme-catalysed reaction mechanisms, including for complex metalloproteins. Some of us have recently studied the substrate binding and the catalysis in pyruvate formate-lyase activating enzyme (PFL-AE), an iron-sulfur-containing enzyme and a member of the radical SAM superfamily, produced by anaerobic gut microbes [1]. This enzyme introduces an unpaired electron to the protein backbone of PFL, the corresponding glycyl radical enzyme (GRE), by catalysing a hydrogen transfer between glycine and adenosyl radical intermediate. Since radical enzymes catalyse some of the most challenging reactions in nature, a better understanding of the mechanism could leverage their applications for biotechnology, metabolic engineering and synthesis of novel therapeutics.



We explored PFL-AE substrate scope and reactivity with MM MD simulations and QM/MM calculations of small peptides that resemble the Gly-loop, and a larger C-terminus that represents a more realistic PFL domain bound to the AE. We showed how GREs converged on glycyl radical formation due to a better conformational accessibility of the Gly-loop, rather than the highest radical stability of the formed peptide radicals [2].

The main challenges in modelling this and other metalloprotein systems are linked to the accurate calculations of the electronic properties of the metal binding sites using high–level QM methods and the ability to sample conformations and dynamics of the system. To meet these challenges, we and others are the QM/MM ChemShell software [3], for predictive multiscale free energy simulations of hybrid transition metal catalysts (in the FEHybCat project). One of the key tasks of this project is to test workflows and contribute to developing and disseminating best practice for accurate modelling of the intermediates and transition states during the catalysis in natural and artificial metalloenzymes that would provide detailed insights into the dynamical free energy landscape which is crucial for the design of new types of hybrid catalysts and reactions.

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Using many-body dissipative particle dynamics to predict the surface tension of pure and mixed systems

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Dissipative particle dynamics (DPD) is a coarse-grained simulation method, which has been successfully applied to systems that are difficult to study using traditional molecular dynamics techniques. This includes systems requiring long simulation times and large length scales, such as surfactant and polymer systems. Coarse graining simplifies molecules by grouping a number of atoms into ‘packets’ or ‘beads’. One of the main drawbacks of DPD is that the bead density of a modelled system is roughly constant across the domain, leading to an inability to simulate vapour-liquid interfaces. This led to the DPD variation of many-body dissipative particle dynamics (MDPD) [1].

MDPD can be used to model systems with varying density, meaning that a surface tension can be calculated. However, as a result of coarse graining, the parameters used in the calculation of force in DPD models are not directly related to the molecular scale. Therefore one requires a parameterisation to map DPD beads to real systems. For standard DPD simulations, many parametrisation schemes exist however, the application of MDPD to modelling real systems is relatively under-researched.

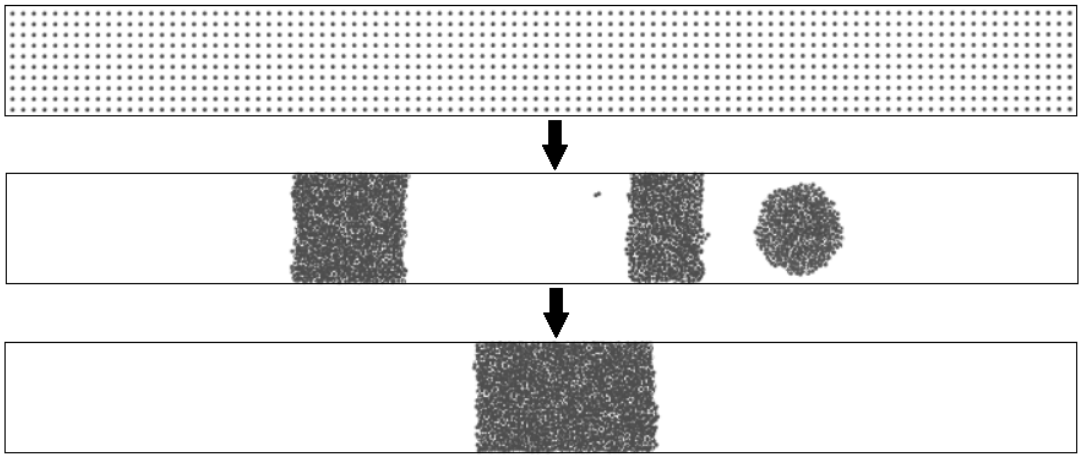

Fig 1. An example of a MDPD simulation that is initialised with random placement of molecules. Molecules are attracted to each other and quickly form coexisting vapour-liquid phases in the same simulation box.

In this work, we present MDPD simulations which have been parameterised to experimental surface tensions and chemical potentials. In order to study the surface properties of pure systems and complex mixtures, accounting for both the surface tension and the mixing properties of simulation components is necessary. In doing so one can obtain the correct behaviours of multicomponent systems. The parameterisation is tested via application to various mixtures, as well as surfactant solutions. The decrease in surface tension that results from surfactant molecules at the water-air interface can be studied, and the surface tension as a function of surfactant concentration compares well with experimental observations. Additionally, values such as the surface area of the interface that each surfactant molecule occupies can be extracted from the simulations and compared with experimental data.

References

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Invited Talk

Modelling the structure of the carbon/electrolyte interface using QM/MD simulations and machine learning.

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The physical-chemistry of the graphene/aqueous–electrolyte interface underpins the operational conditions of a wide range of devices.[1] Despite its importance, this interface is poorly understood due to the challenges faced in its experimental characterization and the difficulty of developing models that encompass its full physics. In this talk I'll present the simulation methods [2-4] we have developed to model such interface also under confinement [5, 6] and how modelling can aid the full characterization of this interface [7, 8].

References

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DNA Damage competes with sequence to pin a plectoneme

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DNA damage is repaired with varying efficiency across the genome. Is this linked to the accessibility of the damage itself? When supercoiled, DNA often forms plectonemes (fig. 1) that protrude out of the densely packed genome to minimise torsional strain. This leads to the hypothesis that damage may locate to the plectoneme tips. If damage does pin the tips, it would reduce the search space for damage-recognising proteins within DNA repair pathways, as well as provide bent or flipped structures for their binding. Therefore, competition for the plectoneme tip may impair DNA repair efficiency.

Certain DNA sequences locate to the plectoneme tips, driven by their intrinsic curvature lowering the energy barrier to form the sharply bent tip. I have designed three sequences with varying degrees of predicted plectoneme pinning propensity. These resulted in a high-pinning sequence, a mid-pinning sequence, and one with no sequence-dependent pinning. This shows for the first time that atomistic simulations can replicate the sequence-dependent pinning seen in experiments and quantify the extent of pinning. Preliminary results supported the hypothesis that there is competition between sequence and damage for the plectoneme tip. Here, I investigate the probability of 1, 2, and 3 bp mismatch pinning in the three constructs, and how the nature of the mismatch also affects the damage-driven pinning. This has been done using implicit solvent all-atom molecular dynamics simulations of 339 base pair minicircles as models for the DNA loops found in the body. The amount of damage required to overcome the differing degrees of pinning changes in the three constructs and may explain why some regions of the genome are repaired less efficiently than others. All 12 possible single mismatch types have been simulated within the no-pinning sequence in order to elucidate structural dependence within the damage itself. Together with sequence, this may have major implications for the rates of DNA repair across the genome.

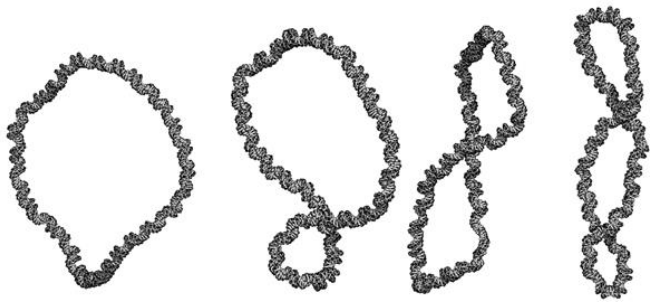

Figure 1: Supercoiled minicircles can adopt a variety of plectonemic conformations even at the same superhelical density. From left to right: open circle, racquet, figure 8, and handcuffs.

Invited Talk

Wetting of Biomolecular Condensates in Biological Cells

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Biomolecular condensates composed of RNAs and/or proteins are formed through phase separation like processes inside cells. There is now increasing evidence that these condensates interact with other cellular components [1,2]. In this talk, I will discuss three examples of such interactions, and how they can be important for biological functions. First, during seed development of the plant Arabidopsis thaliana [3], micrometer-sized condensates form within the vacuolar lumen and wet the tonoplast. Distinct tonoplast shapes arise in response to membrane wetting by condensates. Conditions of low membrane spontaneous curvature and moderate wettability favour droplet-induced membrane budding, whereas high membrane spontaneous curvature and strong wettability promote a membrane nanotube network that sits at the condensate interface. Second, recent observations on the mitochondria of HeLa cells show that protein condensates form in between lipid vesicles [4], and we hypothesise such condensates can provide non-specific capillary adhesion mechanism. Studying the morphology of capillary bridges between a condensate droplet and two vesicles, we find three distinct morphologies, which we term bridging, enclosing and zipping. Each morphology has different force response. Furthermore, we speculate the enclosing morphology can limit molecular exchange from and to the condensates, while the zipping morphology may allow the formation of membrane contact sites. Finally, I will discuss a possible capillary-driven translocation mechanism of HIV capsids through the Nuclear Pore Complex (NPC). This is motivated by recent experiments that show HIV capsids can cross the NPC with their capsid intact, which is remarkable given the capsid is much bigger than the expected passive diffusion limit of the NPC [5]. We speculate that the translocation process is driven by a wetting gradient across the NPC between the cytoplasm-pore condensate and pore condensate-nucleus interfaces. Interestingly, we find that this mechanism can allow the capsid to translocate through the NPC with little to no energy barrier.

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Systematic Design Principles for Combining Rules in Bottom-up Coarse-Grained Interactions

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Systematic bottom-up coarse-graining (CG) of molecular systems provides the means to explore a vast range of length and time scales by treating the molecular-scale physics at a reduced level. However, the configuration dependence of CG interactions often results in CG models with limited applicability for exploring the parametrized configurations. [1] Here, we present two newly developed theories that successfully capture CG interactions across different configurations and conditions, known as "combining rules".

The first approach is inspired by the fact that bottom-up CG interactions are many-body potentials of mean force [1], which are free energy quantities. Hence, a thermodynamically-consistent combining rule is developed by decomposing CG interactions into energetic and entropic contributions. This divide-and-combine approach is shown to achieve chemical transferability for liquid mixtures [2]. Alternatively, the second approach aims to decouple CG free energies spanning a wide range of the conformational space. In turn, distinct classical CG free energy surfaces for characteristic configurations are identified using molecular collective variables [3-7]. The coupling interaction between different CG free energy surfaces can then be determined by an analogy to quantum mechanical approaches for coupled states [8].

The proposed theories can accurately capture the underlying many-body potentials of mean force in the CG variables for various order parameters applied to liquids [4, 6-7], interfaces [5], and proteins. Altogether, these approaches here are expected to facilitate bottom-up CG modeling by uncovering the complex nature underlying the coupling interactions and imparting a new protocol for the design of predictive multiscale models.

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Scipion-EM-ProDy: A Graphical Interface for the ProDy Python Package enabling Integration of Databases, Simulations and Cryo-Electron Microscopy Image Processing

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The ProDy API is an application programming interface that enables protein dynamics analysis from ensembles of structures from experiments and computations through the use of an extensively developed Python package [1,2]. This software provides a broad range of classes, methods and functions that enable the creation of complex pipelines such as normal mode analysis of biomolecular assemblies taking account of their membrane environment [3], SignDy for signature dynamics analysis of protein families [4].

However, despite the existence of a handful of command-line applications and the normal mode wizard (NMWiz) plugin in VMD that provide the core functionalities, the primary method for using this software to date has required a sufficient knowledge of Python to integrate the various classes and functions into useful pipelines as mentioned above. On the other hand is Scipion, an integrative graphical software for combining other software packages into pipelines and workflows, especially for image processing for cryo-electron microscopy (CryoEM) [5].

Several major developments are under way to extract continuous information about protein dynamics from CryoEM data and we are now at the point where an integration between these purely image processing-based methods and structure- and biophysics-based methods is critical. I now present Scipion-EM-ProDy, a plugin for ProDy within Scipion which enables such integration and paves the way for improved methods for extraction of protein dynamics and energy landscapes from CryoEM and simulations.

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Invited Talk

Connecting biological scales – from disease mutations to protein mechanisms through coarse-grained and atomistic simulations

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Proteins conform the ultimate machinery of Life, executing all processes that sustain living organisms – from complex metabolic pathways to neurotransmission. Far from being static, at physiological temperatures, proteins vibrate and cycle between different states or conformers, sensing external signals: in the same way that primary sequences fold into 3D-sructures, each shape encodes intrinsic functional motions of such relevance for life that remain untouched from bacteria to humans. Nevertheless, despite its central role in life, understanding the tight link between protein structure, motion and function i.e. the exploration of protein conformational landscapes, it is still a challenging task. To overcome these limitations, our research integrates coarse-grained path-sampling, ensemble-level analysis and atomistic simulations of "hot" mutations [1-2]. Here we present selected examples where this multiscale approach allowed to dissect the essential motions orchestrating function in highly complex systems, yielding key functional insights validated up to the *in vitro* and *in vivo* level [3-4].

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Simulation of Reactions in Biomolecular Complexes: Blending the Flavours

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We contruct multi-scale simulation frameworks for studies of chemical reactions in proteins. These frameworks combine molecular dynamics with quantum chemical calculations, extended sampling as well as machine learning models. Computational efficiency is increased by application of the semi-empirical density-functional method DFTB3 [1], and trivial parallelisation is achieved with multiple-walker metadynamics [2]. We have been implementing our developments in Gromacs [3, 4], DFTB+ [5] and Plumed [6], including modifications to the corresponding interfaces. Our software is available from an open access repository [7].

The most recent applications are (i) the long-range proton transfer in proteins, like the last proton transfer step in the photocycle of the archaeal proton pump bacteriorhodopsin [8], and (ii) the autophosphorylation of a histidine kinase protein, which constitutes of a large-scale conformational transition in addition to the phosphoryl transfer reaction itself, calling for a truly multi-scale description [9].

Two rather more substantial kinds methodical development have been under development. (i) Both the accuracy and the efficiency of our QM/MM scheme can be improved by applying an additive correction potential to DFTB3 based on machine learning, or even by substituting DFTB3 by an ML model altogether. The goal is to obtain simulation of correlated *ab initio* accuracy for a semi-empirical cost. One of the prospective applications is the simulation of disulphide shuffling processes in proteins, which span largely different spatial and temporal scales [10]. (ii) The QM/MM coupled-perturbed DFTB3 makes it possible to run biased samp ling simulations with collective variables consisting of atomic charges that change during a chemical reaction [11,12]. These will be applied to analyse the mechanism of proton-coupled electron transfer in ribonucleotide reductases and other proteins.

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Free energy profiles of transition metal drug binding from multilevel thermodynamic integration

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The investigation of covalently-binding transition metal based drugs represents an arduous challenge for computational simulations. This is mainly due to two factors: the low accuracy of classical force fields in describing transition metals and their inherent limitations in describing covalent bond formation/breaking. For such systems, hybrid QM/MM simulations [1] are often the method of choice, allowing the treatment of a portion of the system at the QM level, while the rest of the system is represented with a computationally cheaper method, such as an empirical force field.

However, QM/MM molecular dynamics simulations remain a quite expensive method and, in most cases, it would be almost impossible to obtain a full and converged free energy profile of drug binding from the bulk solvent to the target site from QM/MM studies only. This is especially true for large biological systems in explicit solvent, where the binding of multiple drugs and/or multiple target sites need to be investigated. To tackle this problem, we introduced an accurate and efficient multilevel approach for thermodynamic integration, where we combined classical (force field based) and QM/MM constrained molecular dynamics simulations. In this talk/poster, I will discuss the details of this approach, focusing on the subtleties to be taken into account when performing thermodynamic integration at classical and QM/MM levels, and how we merged the different free energy profiles. I will also illustrate an example application, where we successfully applied this method to investigate the binding mechanisms of different transition metal based drugs to multiple sites.

In particular, we applied this method to study different organometallic antitumor agents, based on Ru^{II} and Os^{II} complexes, binding to a nucleosome core particle. Experimental evidence shows preferential binding to distinct sites in histone proteins, but the reasons behind this preference are unclear. The goal of our study was to rationalise the observed selectivity, by elucidating the atomistic details of the binding process in such a complicated environment, i.e. a large protein wrapped by DNA, solvated in water, totalling more than 280’000 atoms treated at MM level, interacting with about 50 atoms treated at QM level.

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Computational Modelling of Gas-Liquid Pickering Interfacial Catalysts Using Dissipative Particle Dynamics

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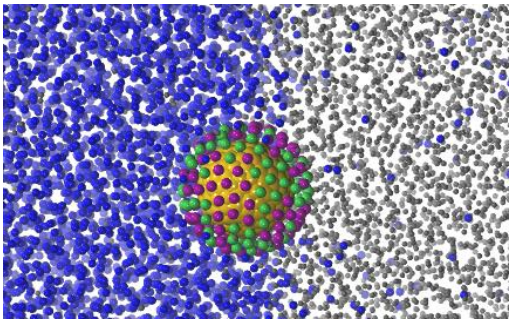
Particle-stabilised (Pickering) emulsions in combination with surface catalytic sites emerge as a promising and greener platform to conduct multiphase chemical reactions. Such strategy allows to create a microreactor environment to efficiently overcome the low contact issue between immiscible phases, which commonly limits the efficiency of multiphase catalysis, and gathers the advantages of both homogeneous and heterogeneous catalysis, including high activity and selectivity, easily phase separation, catalyst reutilisation and compartmentalization of reactants and products. The wetting properties and the local microenvironment around catalytic centres are determined by the nature and distribution of surface groups. Thus, a precise formulation of the surface ligands must be carried out carefully. In this regard, mesoscopic computational techniques offer a convenient and cost-effective way to formulate potential candidates to conduct effective multiphase reactions.[1]

Here, we have carried out a Dissipative Particle Dynamics (DPD) investigation on silica-based Pickering emulsions with -SH groups and fluorinated chains as grafted ligands, stabilized on a gas-liquid interface between an o-xylene/benzyl alcohol mixture and oxygen gas. Firstly, we determined the DPD repulsion parameters using the isothermal compressibility and the Hildebrand's solubility parameters as proposed by Groot and Warren[2] in 1997 and Travis *et. al.*[3] in 2007. Afterwards, following a recently proposed strategy to simulate gas-liquid interfaces by Wang *et. al.*[4], we performed DPD simulations and analysed the behaviour of the nanoparticle at the interface. The distribution of the grafted ligands was changed from random to Janus-like pattern, showing a completely different behaviour, in agreement with the experimental results.



Schematic representation of a nanoparticle stabilised at the interface of two immiscible phases.

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Application of QM/MM Methods to Understand the Role Played by Different Amino Acid Residues in the Catalytic Mechanism of Plastic PET degrading Enzymes

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Plastic accumulation is one of the main environmental issues of our time. In 2016, two enzymes capable of degrading polyethylene terephthalate (PET), one of the most common plastic polymers, were discovered. PETase and MHETase from *Ideonella sakaiensis* (*Is*PETase and *Is*MHETase, respectively) work sequentially to degrade PET to its constituent monomers. PETase catalyzes the cleavage of PET repetitive units ((mono-(2-hydroxyethyl)terephthalic acid (MHET)), whereas MHETase hydrolyses MHET into terephthalic acid (TPA) and ethylene glycol (EG). In this work, the catalytic mechanism of *Is*PETase was studied by QM/MM [1].

The reaction was found to progress in four distinct steps, divided into two major events: formation of the first transition intermediate and hydrolysis of the adduct. The transition state and respective reactant and product of each step were fully characterized and described. The rate-limiting step was found to be step 3, with an activation barrier of 12.5 kcal mol^{-1}. Furthermore, in this study, we have shown the critical role of a triad of residues composed by Ser207, Ile208, and Ala209 in stabilizing the catalytic Asp206 residue. This finding confirms the importance of using a larger QM region since our results disclose some important differences when compared with previous computational studies of the same mechanism. These results provide valuable insights into the catalytic mechanism of *Is*PETase that can contribute to the rational development of more efficient engineered enzymes.

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Mesoscale modelling and simulation of water/poly(ethylene oxide) on silica surfaces

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Understanding how organic additives disperse onto surfaces is important to the key application areas of clean air, fuel cells and green hydrogen. A wide variety of experimental techniques have been applied to probe the structure of adsorbed materials on solid surfaces, e.g Multi-Angle Dynamic light scattering, Atomic Force Microscopy (AFM) and Quartz Crystal Microbalance (QCM). Despite the range of experimental techniques available, such techniques struggle to extract crucial microscopic information such as the precise structural characteristics and chemical composition of adsorbed material. In contrast, computational techniques allow researchers to investigate the microscopic adsorption of additives onto solid surfaces at the atomic resolution and the influence of various different surface features.

Dissipative particle dynamics (DPD) is a coarse grained technique that is increasingly being applied to industrial applications and has been rapidly developing in its ability to predict martials properties, these include studying surfactants, polymers, lipids and many other complex system.[1–4] The advantage of employing this technique is that it allows one to simulate significantly larger spatial domains and longer time-scales compared to atomistic molecular dynamics.

Here we employ DPD simulations to model silica/water/poly ethylene oxide (PEO) systems based on experimental silica/water contact angle and PEO absorption isotherms on silica surfaces. The solid/solvent/additive models allows us to study systematically the effect of surface chemistry on the dispersion of additives at molecular level. We outline the methodology followed to model a range of silica surfaces (crystal and amorphous) with Q^3 and Q^4 surface environment and their interaction with water and PEO. The protocol outlined to model silica/water/PEO system can be applied to model a range of surface/solvent/additive systems.

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Interfacial Free Energies from MD Simulations: Application to $CaSO_4.xH_2O$

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The calculation of solid/liquid interfacial enthalpies using Molecular Dynamics simulations is now routine. But these calculations exclude entropic contributions, which can be an important factor in systems where the solid surface can impose strong ordering in the liquid. What is required is a method for calculating Interfacial Free Energies (IFEs) which include enthalpic and entropic contributions. Such methods do exist but tend to be developed for simple systems and are difficult to transfer to more complex systems [1].

We present a general method for calculating IFEs which can easily deal with complex materials and surfaces, which may also contain miscible species. Our method relies on transforming the solid component of the interface into bulk material via an Einstein Crystal; avoiding the need to define an explicit real-space pathway for the transformation. Furthermore, the method is very efficient as many values may be computed once and re-used for multiple different interfaces [2].

Our method has been applied to the calculation of IFE of different members of the $CaSO_4 \cdot xH_2O$ group of materials with water. This is a particularly challenging system to study due to strong binding between the Ca^{2+} ion and water [3], the inclusion of miscible water molecules which formally belong to the bulk material but may behave as liquids at the interface, and the presence of surface dipoles for the hemihydrate phase (Bassanite, $CaSO_4 \cdot 0.5H_2O$).

Our results indicate that entropy accounts for between 40-90% of the IFE in $CaSO_4 \cdot xH_2O$ systems, in contrast to the NaCl/water interface where entropy accounts for approximately only 20%. We also find that in general the IFEs of Bassanite interfaces ($CaSO_4 \cdot 0.5H_2O$) have a much greater contribution due to entropy than those of Gypsum ($CaSO_4 \cdot 2H_2O$), indicating a possible reason why Bassanite is often observed first during crystallisation from solution [4]. Predicted equilibrium morphologies also show good agreement with previous studies.

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Nucleation of Biomolecular Condensates from Simulations and Experiments in Finite-Size Volumes

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The Liquid-liquid phase separation of polymer and protein solutions plays a vital role in various fields, including synthesising stimuli-responsive materials, synthetic biology, and forming membrane-less organelles in cells. Across these research fields, it is vital to understand the thermodynamics and the kinetics of phase separation, which is initiated by the nucleation of a dense liquid droplet within a lean liquid solution.

The nucleation of (bio)polymer condensates is a concentration-driven self-assembly process. As such, when condensates form in small, isolated volumes, confinement conditions introduce constraints on the thermodynamics and the dynamics of the nucleation process. In extreme cases, confinement in isolated small volumes can suppress the nucleation process entirely [1-3]. When nucleation can still occur despite confinement limitations, it leads to a single, stable droplet of the condensate phase with a well-defined steady-state size [4].

In this talk, I will discuss a general theoretical framework for the interpretation of liquid droplet condensation in small, confined volumes that enables to obtain quantitative information on the thermodynamics and the dynamics of the nucleation process from information on their steady-state configuration [1-3]. In particular, we leverage the fact that, at steady-state, both NVT simulations and microfluidic experiments of phase separation generate a single, stable droplet, corresponding to a local minimum of the nucleation free energy profile.

On the simulation side, I will discuss applying this idea to analyse coarse-grained simulations of two phase-separating systems with different physicochemical characteristics: NDDX4 and FUS [5]. I will then show how a similar approach can be used to interpret microfluidic experiments investigating the behaviour of a phase-separating polymer able to mimic the protein phase separation at different concentrations and temperatures.[6]

While the sources of confinement effects differ between molecular dynamics simulations in the canonical ensemble and experiments performed in microfluidic devices, the approach proposed provides a general, straightforward and efficient route for obtaining emergent thermodynamic and kinetic properties of biomolecular condensates.

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Atomistic Molecular dynamics simulations studies of Water-DMSO mixtures

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Water-dimethyl sulfoxide (DMSO) (Water-DMSO) mixtures are vital to study in relation to their physical and structural properties due to the miscibility of DMSO in water. A physical insight to understand the h-bonding between water-DMSO is crucial to understand the dynamics of water and DMSO molecules. The atomistic simulation studies of water-DMSO mixtures are done using molecular dynamics (MD) simulations to investigate their structural properties. The MD simulations were done at different weight percentages of DMSO, such as 10, 20, 30, 40, 50, 60, 70, 80, 90, and 100. It was found experimentally that the density of water-DMSO mixtures increases with DMSO composition (wt %). It was found in the present study that the number of intermolecular h-bonds between DMSO-water increases with the DMSO composition (weight percent). This agrees with experiments where DMSO showed enhanced miscibility with increased DMSO concentration. The results of the intermolecular structure between water-DMSO will be presented as pair distribution functions between different atomic pairs. Moreover, the transport properties of water and DMSO was investigated as a function of DMSO composition, and results will be presented. The molecular insights obtained through the MD simulations will be crucial to understand the microscopic structure of the water-DMSO mixture, which may be crucial for its usage for a wide range of applications.

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Poster

Reduction pathway of glutaredoxin 1investigated with QM/MM moleculardynamics using a neural network correction

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Glutaredoxins are small enzymes that catalyze the oxidation and reduction of protein disulfide bonds by the thiol–disulfide exchange mechanism. They have either one or two cysteines in their active site, resulting in different catalytic reaction cycles that have been investigated in many experimental studies. However, the exact mechanisms are not yet fully known [1].

In our study, we investigated a proposed mechanism [2] for the reduction of the disulfide bond in the protein HMA4n by a mutated monothiol Homo sapiens glutaredoxin and the co-substrate glutathione. To estimate the regioselectivity of the different attacks, classical molecular dynamics simulations were performed and the trajectories analyzed regarding the sulfur–sulfur distances and the attack angles between the sulfurs. The free energy profile of each reaction was obtained with hybrid quantum mechanical/molecular mechanical metadynamics simulations. For an accurate description, we used semi-empirical density functional tight-binding method with specific reaction parameters fitted to B3LYP energies of the thiol–disulfide exchange. In addition we applied a machine learned energy correction (ΔML) [3] that was trained on coupled-cluster single double perturbative triple [CCSD(T)] energies of thiol–disulfide exchanges.

Our calculations show the same regiospecificity as observed in the experiment, and the obtained barrier heights are about 12 and 20 kcal/mol for the different reaction steps, which confirms the proposed pathway. The computational cost of the ΔML correction is comparable to a DFTB calculation, but offers a potential for higher accuracy and greater flexibility for a somewhat increased computational cost. Due to the extensive phase space sampling, this approach includes environmental effects and the ΔML correction allows to describe correlation effects relevant for the thiol–disulfide exchange reaction, which most DFT-GGA functionals do not capture. Thus we suppose that this approach offers great benefits especially when molecular systems of lager size are studied and correlation effects can not be neglected.

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Poster

Title: A multiscale simulation approach to characterise the glidesome-associated connector (GAC) from *Toxoplasma gondii*

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Apicomplexan parasite is a phylum of parasites which causes a range of diseases in humans and animals, with the most significant being malaria from *Plasmodium falciparum* (Pf) and toxoplasmosis from *Toxoplasma gondii* (Tg). These parasites employ a unique form of substrate-dependent locomotion known as gliding motility to invade host cells, egress from the infected cells and cross biological barriers. Gliding motility is powered by an actin-myosin based motor assembly known as glidesome and a proper connection between F-actin within the glidesome and transmembrane surface adhesins is crucial for the process.

A new protein, termed the glidesome-associated connector (GAC) has been recently discovered which represents the key molecular link that establish the proper connection needed for the gliding motility. GAC is a highly conserved across the entire Apicomplexa phylum and previous low-resolution small-angle X-ray scattering (SAXS) study of TgGAC presented it as a ~27 nm club-shaped molecule that forms complexes with three binding partners (PA lipid, F-actin and surface adhesin) through different motifs [1].

We have recently obtained a new high resolution crystal structure of TgGAC [2] which represents a new closed form of GAC. This unexpected closed state poses new questions about how GAC carries out its role. To help answer the question, we used coarse-grained MD (cgMD) and comparative analysis to gain further insight into the closed form of GAC. We also used steered MD, cg2at backmapping and atomistic MD (atMD) to model the open form, which allowed us to fit the SAXS data better. Overall, our result showed that the closed form could be an important functional state.

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Poster

Multiscale Modelling of Charge Dynamics in Neuromorphic Devices

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A first principle multi-scale model is used to study the charge dynamics of a neuromorphic device based on PEDOT:PSS in an NaCl electrolyte system [1]. We compare the results under the condition of applying an orthogonal electric field and without electric field to study the device operation properties. The coordinates of the sites are used to construct a list of molecule pairs for which a reorganization energy, site energies, coupling elements and Marcus rates are calculated [2,3].

Our results reveal a different energy landscape when an orthogonal electric field is applied to the device. Mobility calculation shows a larger device conductance when Cl- ions are driven into the devices and changes the charge carriers' number. Random walk theory and Kinetic Monte Carlo (KMC) are used to study the fast/slow charge dynamics in the device network. This study explains the linkage between the elementary processes on atomistic/electronic level and the device performance.

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Measurement of ZnO Atomic Distances under Isothermal and Isobaric Ensembles: A Molecular Dynamics Prediction

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Abstract

Zinc Oxide (ZnO) chemical bonds have been stayed between covalent and ionic liaisons; this appears in its thermodynamic behavior and the atomic distances under extended pressure and temperature. In this work, the impact of pressure and temperature is focused on the distance between the atoms of unit cell O-O, O-Zn, and Zn-Zn (1458 atoms of O^{2-} and 1458 of Zn^{2+}) under the range of pressure (0-200 GPa) and temperature of range 300-3000K. Molecular Dynamics technique (MDs) and DL_POLY_4 software are employed on the RAVEN Supercomputer of Cardiff University (UK). The interatomic interactions are modeled using Buckingham potential for short-range and Coulomb potential for long-range. This paper calculates and confirms the effect of pressure and temperature on Zn-O bond length which is less than that on Zn-Zn and O-O bonds, also the relationship of these lengths, standard error, standard deviation, the mean, the maximum values of radial distribution function, the percentage of variation, and finally the validity of Buckingham potential for ionic and covalent chemical liaisons are reported. The obtained results are in the vicinity of available theoretical and experimental data; these results would have a great importance in nanotechnology and technology fields, especially in Medicine and Pharmaceutics.

Keywords: *ZnO, chemical Bond, Pressure, Temperature, MDs*

Poster

Exploring the Mechanism of Autophosphorylation in the Bacterial Sensory System using QM/MM Simulations

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Two Component Systems (TCS) are a fundamental form of signalling transduction pathway found in bacteria and are not present in human genomes, making them a promising target for the development of selective antibacterial drugs. These systems are composed of a sensor kinase, which detects changes in the environment and a response regulator, which initiates the corresponding cellular response. Kinases are a class of enzymes that play a crucial role in various biochemical processes and are a prototypical example of enzymes that use signalling cascades and conformational gated chemical reactions. Histidine kinases (HK) are a common type of sensor kinase found in many TCS. When activated by conformational changes, these HKs undergo autophosphorylation of a conserved histidine residue through a catalytic process.

The membrane-bound HK is a homodimer with each monomer containing a dimerisation histidine phosphotransfer (DHp) domain and a catalytic and ATP-binding (CA) domain. When an extracellular signal is detected, the HK performs an autophosphorylation of a conserved histidine residue located in the DHp domain. Depending on the TCS, one of two different autophosphorylation mechanisms takes place: In cis-HKs, the ATP bound to one CA domain phosphorylates its own DHp domain, whereas in trans-HKs, the histidine of the DHp domain of the other monomer is phosphorylated. The autophosphorylation thereby leads to a protonated phosphohistidine intermediate, which is subsequently deprotonated by a nearby base.

Previous computational studies were unable to capture the complete autophosphorylation mechanism due to the timescale of biochemical reactions, which typically falls within the range of several hundred nanoseconds to microseconds. However, by employing semi-empirical DFTB, which has a computational cost that is 2 to 3 orders of magnitude lower than DFT, we are able to investigate this reaction mechanism in a trans-HK using a QM/MM hybrid enhanced sampling (metadynamics) simulation with different bases on a time scale of up to a microsecond. This simulation provides valuable insights into the detailed mechanism and its free energy landscape, and also allows us to simulate and compare different HK systems with different proton acceptors and compare the outcomes of the simulation with experimental observations.

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Poster

Insights into NLRP3 inflammasome activation using MD simulation

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NLRP3 (NOD-, LRR- and pyrin domain containing 3) inflammasome is a cytoplasmic protein complex that regulates the activation of inflammatory cytokines. Given its implication in a range of diseases, NLRP3 is an important therapeutic target.[1] The cofactor ATP and the centrosomal kinase NEK7 are important for NLRP3 activation (**Figure 1**). We have constructed and simulated computational models of full-length monomeric NLRP3 to shed light on the importance of NEK7 and cofactor interactions for its conformation and dynamics in aqueous solution. These computed dynamical trajectories of NLRP3 provide insight into coordinates of deformation that may be key for cofactor binding and inflammasome activation.[2]

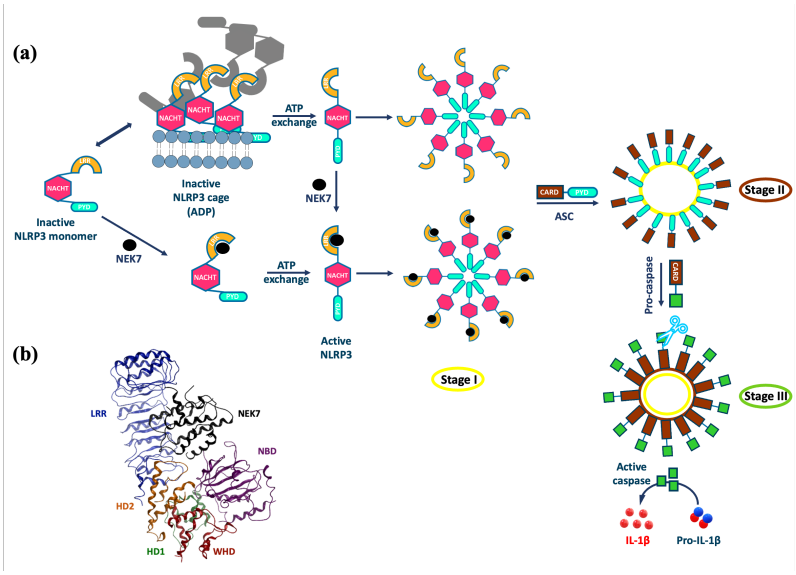

Figure 1. (a) Diagrammatic representation of NLRP3 inflammasome activation: stage I, sensor oligomerization; stage II, $NLRP3^{PYD}$–ASC^{PYD} interaction and formation of ASC filaments; stage III, ASC^{CARD}–$procaspase^{CARD}$ interaction and activation of caspase. **(b)** Cryo-EM structure of NEK7/NLRP3/ADP (PDB code 6NPY)[3].

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Poster

Study of monoclonal antibody formulations to decrease aggregation using molecular simulations

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Therapeutic proteins such as monoclonal antibodies (mAbs) have been approved for the treatment of different kinds of diseases in humans. For a therapeutic protein to be commercially available, the shelf life of greater than 12 months is required, while many mAbs only have a serum half-life of a few days, therefore the stability of mAbs during manufacturing and final storage is vital [1]. The stability can be improved by reducing the aggregation propensity of mAbs. Addition of excipients (such as ions, free amino acids and small organic molecules) is a way to mitigate aggregation. By altering the types and concentration of excipient molecules, the stability can be modified.

We focused on evaluating the formulation for aggregation-prone therapeutic mAbs using atomistic and coarse-grained (CG) cosolvent molecular dynamics (MD) simulations. By defining concentrations of excipient molecules in the storage buffer and molecular composition of the buffers, we can analyse the mixed solvent dynamics and its effect on the protein conformation.

To assess the effect of mixed excipients for antibody formulations, the NISTmAb (a standardised IgGk1 mAb) has been used. The calculated solvation population given by the atomic MD simulation were compared to published biophysical experimental data [2]. A good correlation was found between the radial distribution functions (RDF) of each respective excipient and the second osmotic coefficient (B_{22}) for NISTmAb. B_{22} is a representative of the protein aggregation propensity, suggesting that the excipient molecule population surrounding the protein plays a vital role in aggregation and molecular stabilisation.

The atomistic simulations of the whole mAb are only 50 ns due to system's size, so 1 μs CG simulations of the mAbs are currently ongoing process to check the stability of mAbs in different concentrations of cosolvents in a longer timescale.

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Therapeutic Design For Nasal Powder Delivery

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of the coronavirus disease 2019 (COVID-19) pandemic. The pandemic was hugely problematic on a large scale, claiming over 6.7 million lives globally since 2020 (1), and the immediate response was a focus on the development of novel therapies, which saw the Pfizer/BioNTech (2), Moderna (3) and the Oxford/AstraZeneca (4) vaccines rolled out at speed for emergency use. However, these therapies don't come without the problems associated with traditional vaccines including vaccine hesitancy caused by blood-injection-injury phobia (5).

Molecular Dynamics (MD) simulations allow a detailed understanding of molecular interactions at the protein/surface interface. In this work, I will model the SARS-CoV-2 Spike (S) protein, which facilitates the entry process and infection by the virus, with inorganic materials, and study these functionalised nanoparticle systems. These studies can be used as a basis for the development of alternative vaccines which utilise different administration routes.

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Investigating the Intercalation of Cryptolepine between DNA Watson and Crick Base Pairs

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Cryptolepine, a natural drug produced by the Cryptolepis Sanguinolenta plant, is known for its anti-malarial properties [1,2]. Unfortunately, it is also believed to have cytotoxic properties, making its use to treat malaria in humans difficult [2]. Despite this, interest in Cryptolepine's properties for cancer treatment has sparked interest in further investigation, in particular, we perform computational work on the Cryptolepine's ability to intercalate between cytosine rich sequences in DNA. We seek to understand the mechanism with which the molecule binds between DNA base pairs, specifically cytosine and guanine bases. We also seek to investigate which sites it favours as experimental data suggest that Cryptolepine prefers to bind within certain base pair combinations. This has been investigated by performing DFT calculations using the B3LYP XC-functional and the 6-31g basis set for the DNA with and without the backbone structure. As the Cryptolepine is believed to be stable between the DNA bases via long range interactions through π-π interactions, Molecular Orbital analysis has also been used to investigate the HOMO and LUMO structures of the Cryptolepine-DNA complex. The GD3 correction has been applied to the DFT calculation. We perform molecular dynamics calculations of a DNA structure with explicit water solvent which demonstrate the ability of Cryptolepine to bind within DNA base pairs in biological conditions. Cryptolepine's ability to bias towards certain sites in DNA could play a pivotal role in assisting with cancer treatment with its ability to potentially block it from replicating.

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Quantum tunnelling in methylated DNA

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Methylation is an important process of gene regulation in DNA, which means that the methylation of specific sites of the nucleotides behaves as a signalling for gene expression [1]. Nonetheless, this process can also occur in unintended sites due to the presence of other alkylating agents in the cells that derive from external sources, such as smoking and pollutants [2]. This type of structural change may be implicated in DNA mutations during the process of replication, and if not promptly accounted for by DNA repair mechanisms, may lead to the development of diseases like cancer.

One common example of an alkylating agent is dimethyl sulfate (DMS), which can methylate guanine in the O6 position, giving origin to O6-MeG, considered highly mutagenic. Due to a steric competition in the binding site of double-strand DNA, this purine can pair with thymine, causing a point mutation in DNA [3], or correctly with cytosine but with a missing hydrogen bond [4].

We suggest that not only the tautomerization of base pairs can be an important cause of mutations in DNA, but that tunnelling through the energy barrier of the reaction may also play a part in this phenomenon [5, 6]. Hence, we explored, from a quantum chemical point of view, if the methylation of DNA modifies the probability of tautomerization, and what are the mechanisms behind this process.

We performed DFT calculations to investigate the optimal structures of the O6-MeG-C and O6-MeG-T base pairs and their tautomers. Similarly to what we previously reported for related systems, we employed the B3LYP hybrid exchange-correlation functional and the 6-31G** basis set [7, 8]. We will then examine the transition states leading to tautomerization and discuss the importance of tunnelling effects in these systems. We will extend the calculations to explicitly account for the solvent and local environment through QM/MM calculations.

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Poster

Potential inhibitors for beta-lactamases under the alchemical microscope

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Antimicrobial resistance (AMR) is one of the major global threats to human health [1]. While bacteria have evolved many different resistance mechanisms, the production of enzymes called β-lactamases is the most common mechanism against β-lactam antibiotics, such as penicillin [2]. β-lactamases mediate AMR by catalysing the hydrolysis of the β-lactam ring responsible for the antimicrobial effect of the antibiotics [3]. The resistance of metallo-β-lactamases, such as VIM-2 and NDM-1, to almost all types of β-lactam antibiotics will need to be overcome with combination therapeutics using β-lactam antibiotics and β-lactamase inhibitors [4,5].

Alchemical free energy (AFE) calculations offer a computationally manageable way of obtaining free energies of binding needed in lead optimisation processes of structure-based drug design pipelines [6]. In the current study, we use AFE calculations to confirm experimental results of binding affinities of potential inhibitors obtained from Pemberton *et. al.* [3] against two types of β-lactamases. Our AFE results with MUE 0.76 kcal/mol obtained with KPC-2 show that AFE calculations perform well with serine-β-lactamases. Using our results from quantum calculations, we will assess how current zinc force fields perform in the context of AFE calculations.

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Exciton transfer simulations in light harvesting complexes accelerated by machine learning

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Nature has developed highly efficient photosynthetic units in the course of evolution. In addition to regulatory and quenching tasks, light-harvesting (LH) complexes are responsible for collecting and transmitting the energy of sunlight in the form of excitons, which they accomplish with extremely high quantum efficiency.

In LH complexes, the photoactive pigments are arranged within a protein framework, which prevents the formation of triplet states and protects the pigments from interactions with solvent molecules. Most importantly, this arrangement ensures the specific spacing and alignment of the pigments, which leads to optimized energy transfer.

Non-adiabatic molecular dynamics (NAMD) methods, such as trajectory surface hopping, can be used to simulate the transfer of excitons between different pigments. The motion of the exciton results from the coupling of nuclear and electronic degrees of freedom. Due to the size of biological LH complexes combined with limited computational resources, such simulations are extremely challenging. We aim to integrate machine learning techniques to replace costly quantum-chemical calculations and enable efficient NAMD simulations of exciton transfer in LH complexes.

Here, we present simulations of exciton transfer in the light-harvesting complex II (LH2) of purple bacteria, which are examined in terms of underlying transfer mechanisms, (de)localization, temperature dependence, and transfer timescales. Neural network models are trained for the prediction of transfer Hamiltonian elements using reference data from semi-empirical time-dependent long-range corrected density functional tight binding (TD-LC-DFTB). For the prediction of excitation energies, the models take into account the specific environment of the pigment molecules in form of the induced electrostatic potential.

Mg^{2+}-induced folding and misfolding of ribozyme studied by coarse-grained RNA model

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Many functional RNA molecules need to be folded into specific tertiary structures, in which divalent cations often play critical roles. It is therefore essential to understand how RNA molecules fold, and misfold if any, by the effect of Mg^{2+}. We have developed and applied a molecular simulation model that can efficiently reproduce diverse structural ensembles and kinetics of RNA, considering the effects of both divalent and monovalent ions [1-3].

To investigate how ions interact with RNA and drive folding, we performed extensive molecular simulations of the *Azoarcus* group I intron ribozyme (195 nts.) using the above coarse-grained model. From equilibrium simulations at different concentrations of Mg^{2+}, we showed how specific bindings of Mg^{2+} ions navigate the folding of structural elements in the RNA in order, as Mg^{2+} concentration increases [1]. We found that the ion condensation is highly specific and nucleotide position dependent, even at low Mg^{2+} concentrations at where the ribozyme does not form tertiary interactions [4]. To further investigate the kinetics of folding, we performed ion-jump simulations in which folding reactions were initiated by the addition of 5 mM Mg^{2+} in the unfolded ensemble. Upon addition of divalent cations, the ribozyme folded to the native conformation in ~60% of the trajectories, while a fraction (~15%) were trapped in specific misfolded states. The global folding transition, as measured by the radius of gyration, was consistent with previous time-dependent SAXS experiments. From comparisons between the folded and misfolded trajectories, we discuss the folding pathways, associated with formations of key structural elements driven by specific binding of Mg^{2+} ions. Our result shows that the persistent misfolded states are not a direct consequence of non-native base pairing, but arise mainly from topological frustration caused by incorrect chain positioning where most of the native interactions are compatibly achieved. By analysing the solvation accessible surface area, we confirmed that the misfolded state is consistent with experimental footprint data. We have also analysed the kinetic correlations between nucleotide-specific Mg^{2+} binding and folding of key tertiary interactions, providing us with an in-depth view of the Mg^{2+}-induced folding of the ribozyme.

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Poster

The pioneer transcription factor Oct4 alters chromatin packing

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In every organism the genetic information controlling cell fate and function is stored in the DNA. In the eukaryotic cell nucleus, DNA is folded in a highly compacted, complex structure known as chromatin. The basic building block of chromatin is the nucleosome, a nucleoprotein complex formed by DNA wrapped around an octamer of proteins known as histones. Traditionally, it was thought that transcription factors, the proteins that control gene expression, could not bind to nucleosome occupied regions. Nevertheless, in recent years, it has been shown that a sub-group of transcription factors, named pioneer transcription factors, can bind nucleosome occupied regions [1].

One particularly interesting pioneer transcription factor is Oct4, a master regulator of pluripotency [2] that can reprogram adult skin cells into stem-cell like cells [3]. We have recently shown that Oct4 not only can bind nucleosomes (as previously reported [4]) but is able to interpret and enhance the nucleosome breathing and dynamics at the single nucleosome level [5].

Nevertheless, how the binding of Oct4 affects bigger chromatin structures is still unknown. For studying such systems, we have recently set up simulations using the multiscale chromatin model of the Collepardo group, a model that describes chromatin fibers at a coarse-grained resolution with great chemical accuracy [8]. In this study, we report the first evidence of how Oct4 alters the structure of 12-nucleosome chromatin fibers. Our simulations reveal that Oct4 binds to itself, forming droplets, and then the droplets act as scaffolds to which DNA is bound, significantly compacting the chromatin fibers. This work is the first report of how a pioneer transcription factor can change chromatin architecture at the multi-nucleosome scale.

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Poster

Multi-scale shear flow induced aggregation of Aβ amyloid in interstitial brain space

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The objective of this study is to characterize the aggregation of Aβ amyloid in the complex extracellular brain space. Aggregation of Aβ amyloid in extracellular brain space is known to be one of the main causes of the Alzheimer's disease, a highly impairing neurodegenerative pathology. Despite having a central role in the progression of the pathology, a complete understanding of the microscopic processes of the formation of amyloid fibrils in vivo is still lacking. The brain interstitial space (ISS) is a complex, dynamic environment containing neural cells, blood vessels and filled with the interstitial fluid (ISF) [1]. Nowadays, detailed three-dimensional representation of the brain's intricate geometry are available thanks to new imaging techniques [2]. There is also an increasing amount of studies and experimental evidences that shows the impact of fluid flows on the aggregation processes of proteins [3]. In this work we use a multi-scale approach to simulate the fluid flow and amyloid aggregation in a realistic three-dimensional representation of the ISF. Molecular dynamics simulations of coarse-grained model of the proteins in conjunction with a Lattice Boltzmann technique to treat the fluid medium, allows to take into account hydrodynamic interactions, proved to enhance the aggregation process [4,5], between moving particles and surrounding environment. With this combined approach, the ISF will be treated as an active agent in the processes that take place in the interstitial brain space and will allow us to reproduce the aggregation phenomena on realistic time and space scales. In our study we inquired the effect of fluid flow in simple and complex geometries, so as to consider the effects shear flow and volume fraction have on the movements and the formation of amyloid aggregates. Simulations at higher spatial resolution of smaller portions of the ISS allow us to further gain microscopic insight in the aggregation process.

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Studying the permeation of small molecules in poly vinyl acetate, PVAc

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Polyvinyl acetate, PVAc, can be used as a base polymer for chewing gum formulations. Here, understanding the binding and release of small flavour molecules is important in controlling flavour release. We use all-atom molecular dynamics to model PVAc polymer in the bulk phase and in thin films. Simulations initially tested the performance of the GAFF (General Amber Force Field) [1] and GAFF-Lipid17 force fields with AM1-BCC and RESP charges as models for PVAc in the bulk phase. Simulations show that we are able to provide good quality predictions for the behaviour of PVAc as a function of molecular weight, including densities, solubility parameters and glass transition temperatures. However, tests additionally show that GAFF leads to polymers that are slightly too stiff in comparison with experiment. A combination of GAFF and Lipid17 improves this but reduces the cohesive energy density of the polymer, reducing the polymer solubility parameter. We tested the permeability of a model PVAc film by using potential of mean force (PMF) calculations. A small "flavour" molecule, sorbitol ($C_6H_{14}O_6$), was pulled across the PVAc film from a contacting water region, using umbrella sampling to calculate the PMF for this process. Pulling the small molecules directly into a glassy polymer generates some steric strain. We show how this strain can be relaxed by local heating of the small molecule to relax its local environment prior to umbrella sampling. An automated script has been developed to allow the screening of small flavour molecules in terms of their solubility in PVAc.

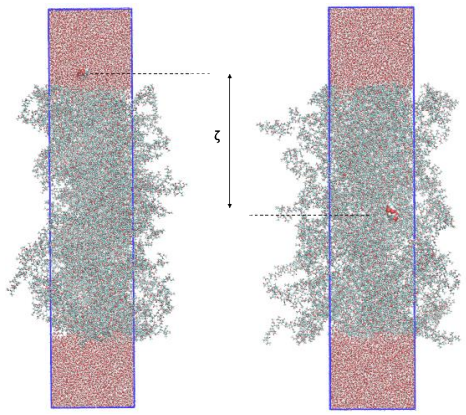

Figure 1. Snapshots of the polymer slab solvated with water molecules at both ends. The initial configuration is shown on the left, followed by the final configuration on the right. ζ is the reaction coordinate

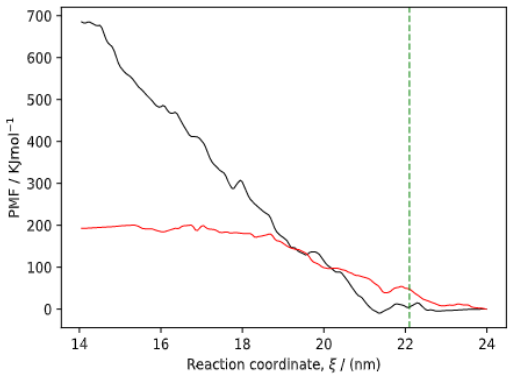

Figure 2. PMF calculated for pulling the sorbitol from the water phase to the centre of the PVAc film without relaxation (black) and with relaxation (red), where dotted green line indicates the interface

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Poster

Towards a realistic multi-scale model of cilia driven clearance

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In this poster, we present our results for a realistic model of cilia-driven mucus clearance in the respiratory tract. The respiratory epithelium is lined with a two-layer fluid meant to protect it from direct contact with inhaled external particles such as dust, viruses or bacteria. The bottom layer is a water-like fluid known as the periciliary layer (PCL), while the layer in contact with air is a high viscosity fluid called mucus in which foreign particles get trapped. The airway epithelial surface is also covered in cilia, motile filaments mostly immersed in the PCL, which exhibit an asymmetric and cyclic beating motion that allows them to push periodically on the overlying mucus layer, thus clearing the lungs from the inhaled pathogens entrapped in it. This transport mechanism, called mucociliary clearance (MCC) constitutes the first line of defence of the respiratory system [1]. In the following work, we use an agent-based model of MCC relying on a phenomenological model for the ciliary beating [2]. The motion of the cilia is simulated using molecular dynamics, and coupled to that of the surrounding fluid, which is evolved using the Lattice Boltzmann method, thus enabling long range hydrodynamics interactions between cilia [3]. We increase the effective viscosity of the top layer of the box, where the mucus is physiologically located, by introducing short peptides to alter the fluid response to cilia motion at this height. By tuning the parameters of this model, we were able to reproduce the physiological space and time scales of MCC [4]. We use this operative framework to simulate a ciliated epithelium in which we introduce various degrees of disorder in the positioning of ciliated cells and in their respective beating directions to study how it affects their pushing efficiency and the directionality of the induced flow motion [5-6]. Finally, we reproduce some pathophysiological conditions, symptomatic of congenital respiratory diseases, or resulting from viral infections, by removing some "dead" cells or rendering their cilia immotile [7-8].

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Poster

Understanding the improved separation performance of asymmetric polymer composite membranes.

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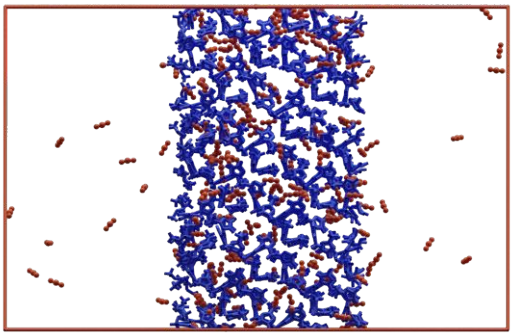
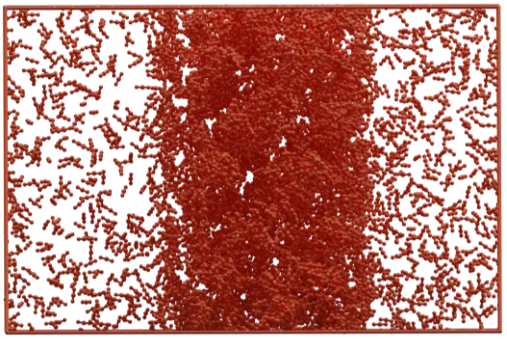
Although polymer films are widely used in gas barrier and separation technologies, pure polymeric materials are limited due to a trade-off existing between gas selectivity and permeability. One option to enhance separation performance is through the addition of filler particles, which can absorb penetrating molecules or increase the effective diffusivity of certain gases. In our research group, we have demonstrated the success of cellulose acetate/ ZIF-67 composite films, which exhibit improved gas permeability and selectivity for CO_2/N_2, CO_2/CH_4, and O_2/N_2. In particular, we have shown experimentally that the performance of composite films can be further boosted through alternative manufacturing processes.

Molecular simulations were performed to explain the observed improvements in barrier performance between ZIF-containing cellulose acetate films prepared through electrospraying (asymmetric membrane), compared to traditional mixing (mixed matrix membrane). Bulk and slab systems of ZIF-67 were generated and validated, before being used as the basis for a cellulose acetate/ ZIF composite model. In this study, the morphology of polymer chains at the interface was compared with those in a neat cellulose acetate bulk system. It was demonstrated that chains were preferentially elongated parallel to the surface, and exhibited lower mobility and higher density in proximity to the ZIF. Conversely to polymer slabs, which show little to no penetration of gas molecules over the course of a molecular simulation, carbon dioxide molecules readily entered and were retained within the ZIF inorganic matrix. We propose that in mixed matrix membranes, where particles are sparsely dispersed, the surrounding rigid, highly dense shell of cellulose acetate blocks oncoming gases, which are instead redirected to surrounding amorphous polymer. In asymmetric membranes, the alignment of particles normal to the gas flux force penetrant gases through the performance enhancing ZIF. Imperfections in the electrospun layer, which appear as gaps between adjacent ZIF particles, are instead plugged by interacting, dense cellulose acetate factions. As particles are closely packed, the option of bypassing the zeolitic framework via amorphous polymer is not possible in asymmetric membranes, resulting in enhanced separation performance.





Poster

Mechanistic properties of DNA govern nucleosome unwrapping

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In eukaryotic cellular nuclei, DNA is tightly packaged into a DNA-protein complex known as chromatin. Chromatin's basic unit is the nucleosome, composed of DNA wound around a core of histone proteins. The spatiotemporal organization of chromatin packaging is one of the key regulators of gene expression [1]. Nevertheless, the physicochemical mechanisms that control said packaging are still unknown, as the study of these properties is challenging due to their multiscale nature.

In this study, we focus on nucleosome unwrapping, which is the process by which the DNA-histone complex is disassembled. The study of nucleosome unwrapping is of great significance, as it can provide insight into a key step in chromatin remodelling, the control of gene expression and chromosomal stability, as well as shedding light on how genes are regulated at the molecular level. Our computational methods, which utilize coarse-grain molecular dynamics simulations, provide an efficient tool to study chromatin at the molecular scale, ensuring a balance between computational cost and accuracy [2].

Our results reveal that mechanistic properties of DNA alone, such as its flexibility, can govern nucleosome unwrapping. Our findings also provide detailed information on the molecular interactions that play a role in nucleosome stability and delineate a multi-scale computational framework that can be used to probe the effect of the mechanical properties of DNA into other mechanisms regarding chromatin organization.

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Poster

Pentacene molecules meet transition metal dichalcogenides for photovoltaic energy harvesting

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Combining two-dimensional (2D) materials with organic materials can be very attractive for applications that require flexibility and where size and weight are important parameters to be considered, such as in wearable, portable and mobile applications. Organic materials usually exhibit excellent optical absorption efficiency and photo- and temperature-induced conformational changes, while 2D materials often show relatively high carrier mobility, superior mechanical flexibility, and tunable electronic and optical properties. Combining both systems can stabilize the organic materials and lead to heterostructures with both high carrier mobility and high optical absorption efficiency, which is promising for solar energy conversion. In this work we investigate, by means of density-functional-theory calculations, heterostructures composed of organic molecules (for example, pentacene and azulene) and transition metal dichalcogenides (TMD) for application in photovoltaic devices. We examine the interaction between the molecules and monolayer TMDs as well as the band alignment of the heterostructures, considering effects of the molecular coverage and dielectric screening.

Poster

Absolute Binding Free Energy Calculations of Monosaccharide and Oligosaccharide Ligands of Concanavalin A

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The ability to predict the affinity of a ligand binding to its receptor is a central problem in computational biophysics and drug design. Recent progress in the computation of absolute free energies has allowed more reliable predictions of binding affinities for druglike ligands to their protein target [1]. Carbohydrates are important protein ligands, implicated in biomolecular recognition and signalling process, and hence understanding their interactions is important for drug and vaccine design. However, these ligands are challenging to model due to their size, flexibility, and polarity [2,3]. Indeed, the application of binding free energy calculations to carbohydrate ligands has been largely limited to computing the relative affinity of monosaccharide-protein complexes. Herein, we utilize absolute binding free energy calculations to predict the affinities of a series of five carbohydrate ligands of increasing size and complexity to the lectin protein, concanavalin A. We consider the ability of the method to qualitatively and quantitatively rank these ligands, which vary from monosaccharides to pentasaccharides, and discuss key factors, challenges, and future directions.

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Poster

Predicting the aggregation of small molecules by molecular dynamics simulation

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Aggregation is the self-association of small molecules in solution at micromolar or sub-micromolar concentrations. Colloidal aggregation of small molecules can be problematic in drug discovery assays. Computational means of identifying and flagging aggregate former compounds in early drug discovery have proved useful. Here, molecular dynamics (MD) simulation is explored as a method to evaluate the ability and extent of aggregation for a set of small druglike molecules. We consider the physicochemical properties of the molecules and the various types of interaction involved in aggregation formation. MD simulation compared favourably with a rule-based cheminformatics approach and provides insight into the basis of aggregation.

Poster

Molecular models of realistic biochars with controlled porosity

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Biochar is a carbon-rich solid material that has seen unprecedented applications in environmental pollution control [1]. Surface functional groups and pore structures play vital roles in the functionality of biochar for the adsorption of various substances: inorganic and organic pollutants [2], [3], gases [4] and nutrients. However, mechanisms governing adsorption processes at the atomic scale cannot be explored from experimental research alone. Molecular dynamics (MD) is a modelling technique that allows the study of materials at the atomistic level. Our work utilises MD techniques to generate realistic biochar models with various surface functional groups and controlled microporosity with the aim of investigating the effect of these properties for the adsorption of pollutants. Models were developed to account for experimentally determined H/C, O/C, aromaticity and true densities of biochars. To control the pore sizes and their distribution, we developed the *virtual atom approach*, where a Lennard-Jones sphere of varying van der Waals radius and softness is used. Its interaction via a soft-core potential with the biochar matrix allows to create pores with rough surfaces, while varying the parameters gives control on the pore-size distribution. We focus on microporosity, creating pores mostly < 2 nm in diameter, and pore volumes in the range 0.05 – 1 cm^3/g. Our approach allows for the creation of molecular models of biochars, representative of realistic systems, accounting for varying surface functionalities and pore-size distributions.

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Poster

Development of Coarse-grained Molecular Simulation Model for Polymer-RNA Nanoparticles

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RNA therapeutics and their delivery mechanisms are a particular focus of research following the success of SARS-CoV-2 vaccines. Polymer nanoparticles are one of emerging and promising delivery mechanism that overcome the problems associated with traditional viral or lipid nanoparticle methods. Despite this renewed interest, very little is known about the microscopic mechanism of formulation and how design alterations to the RNA sequence or polymer structure affect the formulation. We are developing a coarse-grained molecular model to investigate how changes to monomer repeats, molecular weight, and N/P ratio of polymers as well as the RNA structures affect nanoparticle formulations. In the development, we have improved a single-interaction-site RNA coarse-grained model [1] to reproduce experimental thermodynamic stabilities and salt-dependent behaviour of general RNA sequences. For synthetic polymers, a new coarse-grained model has been developed to allow the simulation of RNA-polymer interactions using bottom-up coarse-graining based on atomistic MD simulations. The new model will allow the simulation of the long timescales and large system sizes of nanoparticle formulation and provide the insight needed to improve formulation.

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Poster

Quantum Tunnelling Effects in the Guanine-Thymine Wobble Misincorporation via Tautomerism

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DNA polymerase is an enzyme that catalyzes the synthesis of DNA molecules by matching complementary deoxyribonucleoside triphosphates (dNTP) to the template DNA strand using the standard Watson–Crick base pair rules. However, when a noncomplementary dNTP diffuses into the active site during the polymerase dNTP sampling, the polymerase domain will transition from an open to an ajar conformation, thus forming a different nonstandard hydrogen-bonded base-pairing arrangement called wobble mispair [1]. While there are other sources of replication errors, the fidelity of replication primarily depends on the ability of polymerases to select and incorporate the correct complementary base [2].

Consequently, misincorporating a noncomplementary DNA base in the polymerase active site is a critical source of replication errors that can lead to genetic mutations [3]. In this work [4], we model the mechanism of wobble mispairing and the subsequent rate of misincorporation errors by coupling first-principles quantum chemistry calculations to an open quantum systems master equation [5]. This methodology allows us to accurately calculate the proton transfer between bases, allowing the misincorporation and formation of mutagenic tautomeric forms of DNA bases. Our calculated rates of genetic error formation are in excellent agreement with experimental observations in DNA. Furthermore, our quantum mechanics/molecular mechanics model predicts the existence of a short-lived “tunnelling-ready” configuration along the wobble reaction pathway in the polymerase active site, dramatically increasing the rate of proton transfer by a hundredfold, demonstrating that quantum tunnelling plays a critical role in determining the transcription error frequency of the polymerase.

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Poster

CP-DFTB/MM simulations of tyrosine-tyrosine PCET in RNR-inspired model systems

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Proton-coupled electron transfer (PCET) plays an important role in diverse biological processes, involving organic or organo-metallic cofactors. Prominent examples from nature are the electron transport chain in Photosystem II which is essential for the production of ATP or the 32 Å long radical pathway based on tyrosines oxidation in the enzyme Ribonucleotide Reductase (RNR). An extended sampling method was developed in our group in which coupled-pertubed equations are implemented into the computational favorable density functional tight binding method (CP-DFTB). [1] All prior computational studies on PCET rely on multicale simulations with computational high costly QM methods as DFT, we here propose an alternative workflow using CP-DFTB which allows us to obtain a detailed insight into PCET reactions on longer timescales. CP-DFTB enables the use of Mulliken charges as reaction coordinates to calculate free energies of chemical reactions like PCET, accessing thermodynamic and kinetic properties as well as the principal reaction mechanism. The method has been successfully applied to QM and QM/MM setups including two tyrosine side chains in water. [2] We aim to investigate PCET in biological systems, therefore we start testing the CP-DFTB method on small model systems: β-hairpin peptides [3] and α-helical proteins [4], that are inspired by RNR and have been used for simulating PCET reactions before. [5, 6] One residue in each model system was mutated so that two tyrosines are located in near vicinity, one being fully reduced and the other in oxidized and deprotonated state. MD and QM/MM simulations were performed on length scales suitable to the experimental lifetimes of the radicals [7, 8] and during the simulations the secondary structure of the model systems were preserved. We present here our first CP-DFTB/MM results on a realistic biological system.

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Modelling-Assisted Development of Green Routes to Ordered Mesoporous Silica

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Ordered mesoporous silica (OMS) materials (such as MCM-41) have great potential in a variety of applications such as drug delivery, catalysis and gas separation. However, despite being discovered over 30 years ago [1] the production of these valuable nanomaterials has not been successfully scaled up due to a wasteful and energy intensive synthesis process. Taking inspiration from nature, researchers investigating alternative paths for creating porous silica have discovered greener routes for producing porous silica rapidly and under ambient conditions [2]. However, the formation mechanism of bio-inspired silica (BIS) is poorly understood compared to traditional OMS, hindering control over material properties, in particular the degree of pore order and monodispersity of pores. Critically, there are few computational studies of the synthesis of bio-inspired porous silica, particularly when compared to studies on OMS [3]. Here, we attempt to bridge the gap in understanding between OMS and BIS by applying state-of-the-art multi-scale modelling techniques which have previously been used to investigate OMS synthesis [4] and extending these to include the presence of bio-inspired additives which direct silica deposition during BIS synthesis.

A coarse-grained model based on the Martini 3 [5] framework is presented, which describes the dynamic self-assembly of a supramolecular template around which mesoporous silica forms rapidly in the presence of bio-inspired additives. This model, which is developed and validated using a multi-scale approach, is capable of describing this synthesis under a variety of conditions including the critical range of pH values. Through a combination of coarse-grained and atomistic simulations, we are able to better understand the interaction mechanisms between bio-inspired additives and the evolving silica/surfactant mesostructured, and clarify how the former can direct structure formation. These simulation results help to explain our experimental observations and highlight crucial links between synthesis conditions, mechanistic understanding, and material properties, paving the way for the design of more sustainable routes for producing mesoporous silica.

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Poster

Turning up the heat: understanding of the sensitivity of NLRP3 inflammasome to elevated temperature

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The NLRP3 inflammasome, which drives diverse inflammatory diseases, is activated by a wide range of stimuli, including temperature. Recent studies suggest that NLRP3 inflammasome plays an important role in the pathophysiology of heat stroke, and NLRP3 ablation promotes tolerance in heat stroke pathology by inhibiting IL-1β-mediated neuroinflammation. We found that increased temperature destabilises NLRP3, making it prone to misfolding and aggregation, but the mechanism of this increased temperature sensitivity of NLRP3 remained unclear.

Using all-atom molecular dynamics (MD) and hybrid elastic-network Brownian dynamics (eBDIMS) simulations we found that increasing the temperature promotes an open conformation of NLRP3, which is a step preceding inflammasome activation. This conformational change was facilitated by loop-to-helix transition of the central "core" of NLRP3-unique FISNA domain. However, in the open (active) conformation of NLRP3 at increased temperatures, the FISNA "core" helix unfolded and transitioned to aggregation-prone beta-sheet conformation.

The introduction of specific mutations stabilising helical conformation of FISNA core, and the deletion of the FISNA core both resulted in the protein being predicted to be less prone to aggregation at increased temperatures, yet retaining all key functions of wild-type NLRP3. Our results strongly indicate that the "core" FISNA segment, unique to NLRP3, is key for the unique temperature-sensing properties of NLRP3 inflammasome.

Poster

Efficient pipe interface between the Amsterdam Modeling Suite and external software

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Multiscale modelling often requires coupling multiple components from different software packages to evaluate different levels of theory or to drive the calculation. This is typically implemented by passing input and output files around. However, the associated overhead of I/O operations and process start-ups is significant and becomes a major bottleneck when fast approximate potentials are used. The ideal alternative would be to directly link the necessary software libraries into a single program. Unfortunately, this is frequently infeasible due to technical incompatibilities or licensing restrictions.

To resolve this issue, we have designed an efficient communication protocol to connect two separate processes through a pair of data pipes. One of these processes then repeatedly calls routines exported by the other process, for example to evaluate a potential, perform a geometry optimization, or run a molecular dynamics simulation. Either role can be served by the Amsterdam Modeling Suite or external software. This setup makes it easy to combine the AMS driver with various external potentials or to couple fast potentials such as ReaxFF or GFN-xTB with external drivers. This approach avoids all the pitfalls of direct linking while introducing negligible overhead.

The communication protocol [1] is extensible, future-proof, portable and fully open, providing a reliable mechanism to connect independently developed components without potential compatibility issues. The interface can be easily accessed from Python code based on the libraries ASE and PLAMS. Additionally, a permissively licensed open-source library [2] with interfaces for C, C++, and Fortran further simplifies the integration of the pipe interface into other software packages.

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Poster

Investigation of Heavy Water Effect on Ion Selectivity in ASIC1

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Acid Sensing Ion Channels (ASICs) are proton-gated ion channels selective to cations with a higher selectivity toward sodium (Na^+) compared to the other cations. They are involved in several important physiological roles [1-2]; hence they are one of the most studied channels of the Epithelial Sodium Channel/Degenerin (ENaC/DEG) superfamily. The ASIC1 subunit can function as a homotrimeric channel and its structure is currently the most established of the whole ENaC/DEG family [2-6]. By computing the single ion free energy profile on different ASIC1 structures, we recently showed that the channel is indeed cation-selective and that the histidine of the conserved 'HG' motif from the re-entrant loop plays an important role for binding Na^+ [7]. Based on these results, we investigated ion selectivity by computing single ion free energy for other cations as well as computing the binding energy using Free Energy Perturbation (FEP). Finally, because cations are partially hydrated in the selectivity filter, we investigated the effect of heavy water using the TIP3-HW model. Our results suggest that ASIC1 is more selective to Na^+ than K^+. Furthermore, switching from normal water to heavy water lowers the affinity of Na^+ in the ion binding site. These results match our experimental results and highlight the significant role of the water shell surrounding the cation for ion permeability and selectivity.

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Poster

Developing Standardised Modelling Workflows for Multiscale QM/MM Studies of Metal Oxides

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Modelling plays a key role in advancing our understanding of materials and their properties, assisting in both the development of applications for current materials and the discovery of novel condensed phase systems. The deployment of modelling techniques in this endeavour dictates that models of solid state materials need to be both accurate and efficient, however there is often a compromise between accuracy and computational cost. QM/MM (Quantum Mechanical/Molecular Mechanical) multiscale simulations achieve this accuracy with good computational efficiency by limiting the full quantum mechanical calculation to a small region of interest, where preserving physicality is critical as bonding could be subject to changes; the interaction with the quantum region is then modelled though coupling to an environment of classical charges.[1] This method has advantages over periodic density functional theory (DFT) simulations as these methods are resource inefficient and scale poorly with increasing sizes of cells and require corrections for nonphysical interactions, such as defect interactions that would not be occur at the dilute limit due to limitations in cell size.[2]

We have performed calculations on neutral and charged defects in bulk MgO, employing QM/MM simulations and validating these against periodic DFT calculations in order to develop a full workflow for producing both accurate and realistic models. Our initial methodological development is based on the relatively simple system of bulk magnesium oxide (MgO) in order to facilitate accurate model development due to the wealth of knowledge on the material and its properties, allowing us to design heuristics for easily setting up embedding simulations.[3-6] Specifically, we are exploring the optimal size/shape of the QM and MM regions for accurate and efficient simulation, building on previous work in this area that shows the limitations of the currently applied radial partitioning method and suggests using a unit cell based partitioning approach.[8, 9] The outcomes of this will show if the best method of partitioning can be rigorously identified from chemical observables of the bulk periodic system. In the future, we hope to use this work to investigate species that are more challenging to model, such as titania, for their applications to photocatalytic hydrogen production.

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Plus and minus ends of microtubules respond asymmetrically to kinesin binding by a long-range directionally driven allosteric mechanism

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Although it is known that majority of kinesin motors walk predominantly toward the plus end of microtubules (MTs) in a hand-over-hand manner, the structural origin of the stepping directionality is not understood. To resolve this issue, we modelled the structures of kinesin-1 (Kin1), MT, and the Kin1-MT complex using the elastic network model and calculated the residue-dependent responses to a local perturbation in the constructs. Kin1 binding elicits an asymmetric response that is pronounced in α/β-tubulin dimers in the plus end of the MT. Kin1 opens the clefts of multiple plus end α/β-tubulin dimers, creating binding-competent conformations, which is required for processivity. Our findings explain the directionality of kinesin stepping. [1]

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Poster

Cytotoxic Ag-NHC complexes as LDHA inhibitors

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A potential therapeutic strategy in the fight against cancer is to target its metabolism. It is known that cancer cells preferentially produce ATP via glycolysis, regardless of oxygen concentration (Warburg effect) [1]. Lactate dehydrogenase enzyme plays a key role in glycolytic ATP production, with lactate dehydrogenase A (LDHA) catalysing the forward conversion of pyruvate-NADH to lactate-NAD+, lactate dehydrogenase B (LDHB) catalysing the reverse [2]. Hereditary deficiency of LDHA in humans yields issues only after strenuous exercise (myoglobinuria) [3], and by analogy may be a relatively safe target with no other deleterious side effects. LDHB enzyme has been linked with aggressive cancer phenotypes [4], but LDHB is composed of subunits highly expressed within heart cells and this presents potential undesirable cardiotoxicity (LDHA subunits are expressed mainly in skeletal muscle cells) [5]. Accordingly, inhibition of human LDHA provides an attractive therapeutic strategy in the fight against cancer. A panel of organosilver complexes have been prepared by collaborators at the University of Leeds (recently moved to University of York), and their differing experimental LDHA inhibitions determined. A key aim of my PhD work is to provide a theoretical explanation of how these complexes can be used as LDHA inhibitors via the use of *ab initio* quantum mechanics, molecular dynamics, molecular docking, and free energy calculations to determine types and strengths of binding within LDHA. Repeating our *in-silico* efforts against LDHB aims to determine potential LDH-A vs -B isoform specificity. These results, in tandem with experimental LDHA inhibition data, will potentially provide insights into how the specific chemistries of the complexes improve or impair their use as anti-cancer drugs, with a view to suggesting improvements and ultimately developing novel LDHA specific inhibitors.

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Poster

Using molecular dynamics simulation to predict the aggregation propensity of monoclonal antibodies formulations & accelerate development

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Protein aggregation is one of the biggest challenges in the pharmaceutical manufacturing area, for it largely affects the efficiency of antibody drugs and causes financial loss [1]. Aggregation is increasingly thought to occur through the partial unfolding of protein structure to expose sites that are more prone to self-interaction. Overall, the self-association of proteins is influenced by a combination of surface properties that determine colloidal stability and propensity for surface interactions, the extent and kinetics of global and local unfolding, and the solvent accessibility and aggregation-propensity of local sequences [2]. All of these are modulated by the physical environment provided by the formulation, which can thus alter both the kinetics and dominant pathways of aggregation.

Identifying the specific influence of formulations on aggregation kinetics and mechanism for a given protein, requires considerable experimental characterisation [3], while few generalities can be reliably used in the design of formulations for new proteins of interest. There has been considerable recent growth of experimental characterisation of protein aggregation mechanisms in a range of formulations, and an increased role of computational molecular dynamics simulations to provide insights into the molecular events that lead to aggregation [4].

Building on this, there is now significant potential for computational approaches to begin to predict the impact of formulations on protein stability and aggregation [5]. Hence, the aim of this project is to develop a workflow of molecular dynamics (MD) simulation approaches and artificial intelligence (AI) that can provide molecular-level insights into the aggregation behaviour of mAbs observed experimentally in a range of conditions, including variation in pH, temperature, freeze/thaw or other stressors, and the presence or absence of stabilising excipients. This will also validate the computational approaches and build confidence in their use for predictive purposes. As for the methodology, first of all, all-atom molecular dynamics simulations under different environmental parameter settings (temperature, pH, ionic strength) will be implemented on a Fab domain, which will then be followed by coarse-grained simulations on full antibodies with at least two copies introduced into the system. The data from MD simulations such as RMSD, RMSF, along with the protein sequence and structure information, will serve as the input for the subsequent machine learning process. The combination of MD and AI will offer an opportunity to predict protein stability without additional laboratory work that has been proved to be time-consuming and uneconomical.

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Poster

The replisome environment and DNA point mutations: multiscale simulations of G-C tautomerism and PcrA Helicase

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Proton transfer between the DNA bases can lead to non-standard, potentially mutagenic tautomeric forms [1, 2]. Suppose the tautomers successfully pass through the replication machinery. In that case, they are thought to adopt a Watson-Crick-like shape and mismatch with the wrong base, thus evading proofreading and potentially leading to replication error[3]. There is heated debate over the true biological impact of the tautomeric forms.

Previously it was proposed that if the tautomeric lifetime is much shorter than the helicase cleavage time, no tautomeric population would successfully pass the enzyme[4]. In our previous work, we have determined that the proton transfer energy landscape drastically changes during the first two Angstrom cleavage of the base and indicate that cleavage time is much quicker than previously thought[5]. These results suggest that a static picture of the proton transfer oversimplifies the biological event.

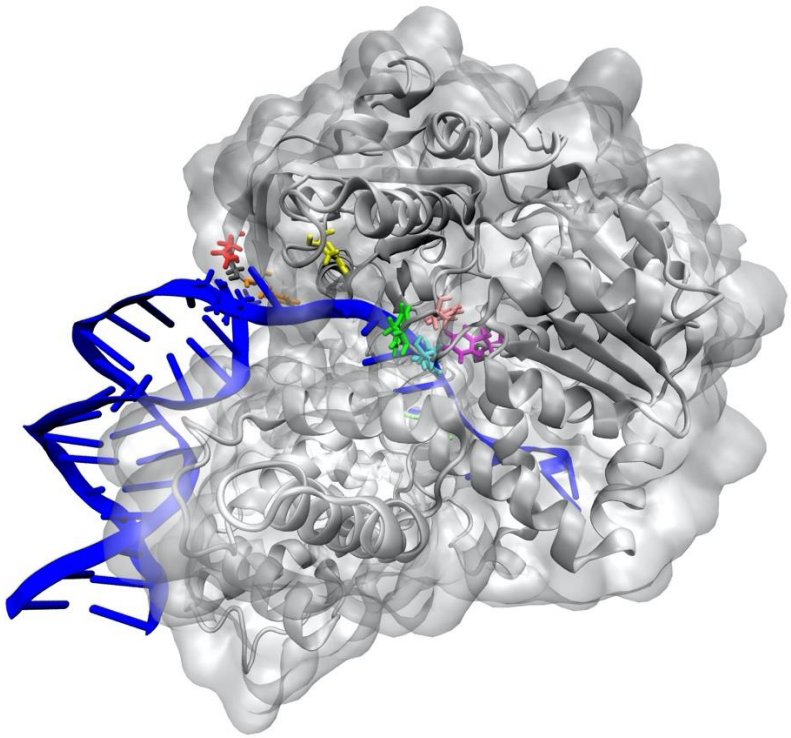

Figure 1: DNA bound to the helicase enzyme. One DNA strand can be seen being pulled through the enzyme. While key residues in the helicase are highlighted.

PcrA helicase (Figure 1) has been well studied in terms of its stepping motor action dynamics[6, 7] and individual amino acid roles in unwinding DNA[8]. Thus PcrA Helicase provides an ideal scenario within which to consider the stability of the tautomeric G*-C* pairing. To further elucidate the complicated environment in which tautomers may be formed, and the dynamics in which they must survive, we employ multiscale quantum mechanics / molecular mechanics (QM/MM) calculations which marry the accuracy of DFT with the large-scale dynamics of MD. The tautomerisation reaction is mapped using Umbrella Sampling to obtain a potential of mean force for DNA in complex with PcrA Helicase for the first time. Understanding the role of the local amino acids at the DNA binding site of this replisome enzyme sheds new light on the feasibility of L¨owdin's hypothesis inside a realistic biological environment. We find that the presence of the helicase, radically destabilises the mutagenic conformations, indicating that it is the first line of defence against spontaneous mutation.

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Mechanistic Investigation of the Androgen Receptor DNA-Binding Domain and Modulation via Direct Interactions with DNA Abasic Sites: Understanding the Mechanisms Involved in Castration-Resistant Prostate Cancer

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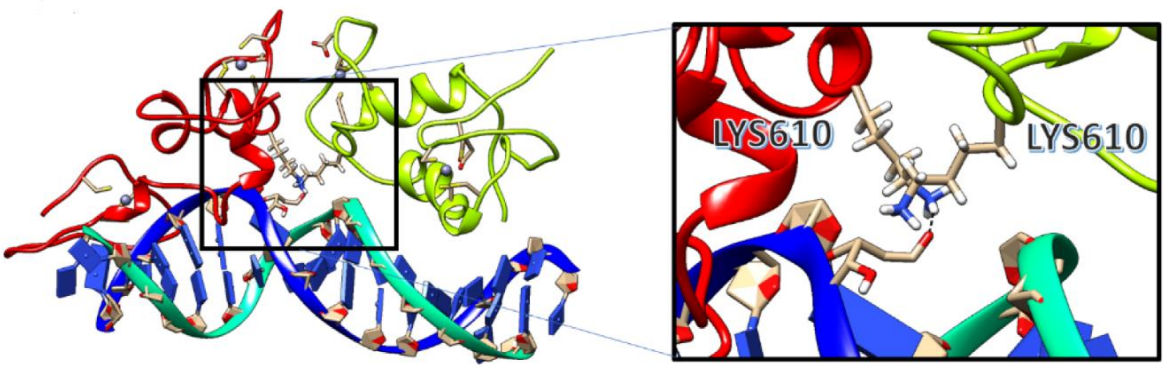
The androgen receptor (AR) is one of the primary drug target in prostate cancer and a driver of castration-resistant prostate cancer. To get a better understanding of how AR binds mutated DNA sequences and how mutations within the protein and DNA regulate AR-DNA interactions, atomistic molecular dynamics simulations and quantum mechanical methods were implemented. Moreover, our results strongly suggest that those abasic lesions may form reversible covalent crosslinks between DNA and lysine residues of an AR via a Schiff base. In addition to providing an atomistic model explaining how protein mutations within the AR DNA-binding domain affect AR dimerisation and AR-DNA interactions, our findings provide insight into how somatic mutations occurring in DNA non-coding regions may activate ARs. These mutations are frequently observed in prostate cancer and may contribute to disease progression by enhancing direct AR-DNA interactions.



Binding and mode of action of the ectoparasite Fluralaner to the GABA RDL receptor of insects.

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γ-aminobutyric acid (GABA) receptors are classified as pentameric ligand-gated chloride channels (pLGIC) and are involved in fast synaptic inhibition in the nervous system. When the neurotransmitter GABA is released from the pre-synaptic membrane of neurons, it binds to the extracellular domain of the receptor, and it induces a conformational transition of the channel which allows the permeation of chloride ions across the cell membrane. In insects, the GABAergic function is mediated by resistant-to-dieldrin (RDL) GABA homopentamers, which are well-established targets of insecticides [1][2]. Non-competitive GABAR antagonists (NCA) act in disrupting the physiological function of GABARs, by binding to a site that is distinct from the agonist binding site. Fluralaner is a third-generation NCA antagonist and is currently used as an ectoparasite against fleas and ticks [2], but not much is known about its binding site and its mode of action. Data obtained from two-electrode voltage-clamp (TEVC) electrophysiology on the GABA RDL receptor of the asiatic rice borer (Chilo Suppressalis) have revealed key amino acids in the protein transmembrane domain that govern the receptor's sensitivity to fluralaner. In this study, we aim to gain an insight into the mechanism of action of fluralaner by combining homology modelling, docking and molecular dynamics simulations. Given the lack of an experimentally-resolved structure for the Chilo Suppressalis GABAR, we have developed and tested an RDL GABAR model homopentamer and have successfully docked fluralaner in the transmembrane subunit interface binding pocket. Molecular dynamics simulations of the protein/ligand complex with fluralaner in the most promising binding poses –as assessed from docking- have shown that the insecticide remains stably bound in the binding site and have revealed key interactions with the protein that are involved in its stability. Mutagenesis of the key amino acid G319 to methionine has been found to obstruct the entrance of the binding site thereby inhibiting fluralaner from binding. This multi-step computational approach has allowed us to rationalise the experimental observations and can contribute to better understanding of the function of this class of NCA.

References

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