Poster #30 **online**

Learning to Bind: In Silico Ligand Optimization via Adaptive Learning of Computed Binding Free Energies

Presenting author: **Yuriy Khalak**

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Co-author/s: Vytautas Gapsys, Bert L. de Groot

Over last two decades development of machine-learning algorithms has made quantitative structure-activity relation models increasingly more accessible. In particular, active learning, an iterative approach, has generated a lot of interest in the pharmaceutical industry, allowing for screening of large chemical libraries for active ligands with relatively few evaluations of ligand affinity. To illustrate the effectiveness of active learning, we apply it to lead-optimisation of phosphodiesterase 2 inhibitors. We use non-equilibrium free energy calculations to estimate ligand binding, which we use as the ground truth for training the models, allowing for a completely in silico approach. In the early iterations we focus on ligand variety to establish promising regions of chemical space. Later iterations search for more optimal ligands within those regions. This strategy yields several potent inhibitors of phosphodiesterase 2. We also quantify the efficiency of our protocol by applying it to a retrospective dataset with available experimental affinity measurements for the same protein.

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Poster #150 **on-site**

GROMACS in the Cloud: A Global Supercomputer to Speed up Alchemical Drug Design

Presenting author: **Carsten Kutzner**

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Co-author/s: Christian Kniep, Austin Cherian, Ludvig Nordstrom, Helmut Grubmüller, Bert L. de Groot, Vytautas Gapsys

We assess costs and efficiency of state-of-the-art high performance cloud computing and compare the results to traditional on-premises compute clusters. Our use case are atomistic simulations carried out with the GROMACS molecular dynamics (MD) toolkit. Biomolecular simulation is a challenging example of a compute-heavy scientific application that spans the whole range from high performance computing (HPC) to high throughput computing (HTC), depending on the questions addressed. Whereas HPC typically aims at a minimal time-to-solution for a single simulation, in HTC, the combined output of many independent simulations is maximized.

We set up an HPC cluster in the Amazon Web Services (AWS) cloud that incorporates various different nodes (or instances) with Intel, AMD, and ARM CPUs, some with GPU acceleration. Using representative biomolecular simulation systems we benchmark how GROMACS performs on individual instances (for HTC) and across multiple instances (for HPC scenarios). Thereby we assess which in- stances deliver the highest performance and which are the most cost-efficient ones for our use case.

We find that, in terms of total costs including hardware, personnel, room, energy and cooling, producing MD trajectories in the cloud can be about as cost-efficient as an on-premises cluster given that optimal cloud instances are chosen. Further, we find that high-throughput ligand-screening can be accelerated dramatically by using global cloud resources. For a ligand screening study consisting of 20,000 independent simulations or 200 µs of combined simulation trajectory, we used all the hardware that was available in the cloud at the time of the study. Using more than 10,000 instances, 140,000 cores, and 3,000 GPUs around the globe, our simulation ensemble that would normally take weeks to complete on a typical on-premises cluster consisting of several hundred nodes, finished in about two days in the cloud. We demonstrate that the costs of such and similar studies can be drastically reduced with a checkpoint-restart protocol that allows to use cheap Spot pricing and by using instance types with optimal cost-efficiency.

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Poster #155 **on-site**

Entropy of Water in Protein Condensates

Presenting author: **Saumyak Mukherjee**

Ruhr University Bochum, Department of Theoretical Chemistry, The Molecular Simulation Group, Bochum, Germany

Co-author/s: Lars Schäfer

The link between the dynamics and entropy of water and protein concentration in biomolecular condensates is investigated with all-atom MD simulations. We compare two different systems, a globular protein [γ-crystallin] and an intrinsically disordered protein [the Low Complexity Domain (LCD) of Fused in Sarcoma (FUS) RNA-binding protein]. The simulations quantify the connection between protein concentration and water entropy, and unravel the underlying mechanisms. These findings provide detailed insight into one key thermodynamic driving force of liquid-liquid phase separation of proteins.

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Poster #179 **on-site**

Nanomechanical Crowding at the Interface between RNA and Soft Surfaces

Presenting author: **Horacio V. Guzman**

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Co-author/s: Simon Poblete, Matej Kanduc, Rudolf Podgornik

Nanomechanical crowding remains theoretically unexplored at the interface of RNA molecules and soft surfaces. Existing RNA molecular models tend to reach very complex ensembles on themselves to be combined to e.g. soft matter mechanics. Here, we introduce a multiscale approach which couples a tractable RNA coarse-grained model [1] with an elastic energy component. Within this approach, we study the specific role of RNA's secondary structure patterns on the deformation of soft surfaces by characterizing representative RNA motifs. First, we study the specific role of RNA stem-hairpin and multibranch secondary structure motifs on its adsorption phenomenology [2]. Under controlled molecular crowding conditions we analyze the effects of conformational entropy and the interplay between surface energy per monomer and deformation lengths. Our findings add a novel way to address the mechanisms of response of encapsulated RNA inside crowded macromolecular environments, like the ones faced during RNA delivery.

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Poster #185 **on-site**

Evaluating the Inhibition of CYP450 Enzyme by Theoretical Chemistry and Machine Learning

Presenting author: **Amin Alibakhshi**

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Co-author/s:

Prediction of CYP450 inhibition by potential drug candidates is a mandatory consideration in drug discovery, due to the crucially important role of these enzymes in metabolizing the drugs and in general chemicals, in the human body. Inhibition of CYP450 by potential drugs can result in their accumulation in the body and increase the risk of drug-drug interactions. In the present study, we develop machine-learning models to predict inhibition of CYP450 1A2 as one of the important CYP450 members present in the liver. For that purpose, we employ the Implicitly Perturbed Hamiltonian (ImPerHam) as a class of versatile representations for more efficient machine learning of challenging problems in molecular sciences, recently proposed by us. ImPerHam representations are defined as energy attributes of the molecular Hamiltonian, implicitly perturbed by a number of hypothetic or real arbitrary solvents based on continuum solvation models. We demonstrate the outstanding performance of machine-learning models based on ImPerHam representations for the challenging case of predicting inhibition of the CYP450 enzyme.

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Poster #195 **online**

Role of Biophysical, Mathematical and Informatics Methods and Tools in Studying Plant Growth and Development: A Case Study of Sunflower

Presenting author: **Maamar Boukabcha**

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Co-author/s:

The growth and development of plants is a very important biological phenomenon among the living complexes biological systems. To study this phenomenon during growth and development, we use several tools, including biophysics, mathematics and informatics. The computer simulations of plant growth have a long history, the simulation of the results data of the growth and development of the sunflower plant by computer software plays an important role to analyze and discuss the different consequences in this work. The measurement and evaluation of parameters by biophysical and mathematical tools play an important role in modeling and simulation in the different phenomena of the growth and development of plants and especially the sunflower plant as an example in our work.

Keywords: Plant growth, Sunflower, Biophysical tools, Simulation, Modeling.

Poster #203 **online**

In Silico Investigation of Membrane-Embedded Aβ Oligomers Highlight the Effect and Specificity of Pore Formation along β-Sheet Edges

Presenting author: **Dirk Matthes**

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Co-author/s: Bert L. de Groot

Oligomeric aggregates of the Amyloid-β (Aβ) peptide are regarded as pivotal agents and primary cause of cytotoxicity related to membrane damage in Alzheimer's disease. Ciudad et al. recently made available for the first time structural data of Aβ(1-42) pore-forming oligomers in membrane mimicking environment. Yet, there are remaining questions on the prerequisites and details of the pore formation process in the presence of membrane inserted β-sheet oligomers with open edge β-strands. Here we used Aβ(1-42) oligomers in POPC bilayers as a putative model system to study lipid-stabilized pores and report results from extensive atomistic molecular dynamics (MD) simulations. Based on the experimental structure template, we investigated various aggregate topologies and sizes in systematic fashion. We found that the formation of edge conductivity pores is strongly dependent on the membrane insertion of the N-terminal residues H13 to K16 and thus on subtle differences in the overall stability, orientation and conformation of the transmembrane β-strand domain. By comparing to the behavior of Aβ truncation variants and Aβ oligomers with unpaired transmembrane β-sheet edge topology, we demonstrate that only β-sandwich structures with parallel sheet pairs and membrane embedded, hydrophilic strands are able to maintain continuous and highly hydrated pores. Backbone carbonyl oxygen and polar side chain atoms from these edge strands were found to critically contribute directly to the coordination sphere of the permeating ions in the center most part of the bilayer. Simulations of oligomers with point mutations either destabilizing or altering the hydrophilic character of the β-sandwich edge structure, furthermore highlight its role as key structural element that defines the properties of edge conductivity pores.

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Poster #205 **online**

Martini 3 Model of Cellulose Microfibrils: On the Route to Capture Large Conformational Changes of Polysaccharides

Presenting author: **Adolfo B. Poma**

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Co-author/s: Rodrigo A. Moreira, Stefan A. Weber

High resolution data from all-atom molecular simulations is used to parametrize a Martini 3 coarse-grained (CG) model of cellulose I allomorphs and cellulose type-II fibrils. In this case, elementary molecules are represented by four effective beads centred in the positions of O2, O3, C6 and O6 atoms in the D-glucose cellulose subunit. Non-bonded interactions between CG beads are tuned according to a low statistical criterion of structural deviation maintaining the Martini 3 type of interactions and are capable of being indistinguishable for all studied cases. To respect the crystalline structure of each single cellulose chain in the microfibrils, elastic potentials are employed to retain the ribbon-like structure in each chain. We find that our model is capable of describing different fibril-twist angles associated with each type of cellulose fibril in close agreement with atomistic simulation. The thermal stability of the fibrils is assessed by our CG model and it defines cellulose I as the most stable structure among all cases in consistency with experiments. This model is supposed to take advantage of the versatile library of biomolecules (i.e. protein, sugars, lipid, etc) present in Martini 3 to design more complex systems which can address large conformational changes such self-assembly of cellulose in cellular plant environment.

Poster #228 **on-site**

Predicting Radical Migration in Collagen

Presenting author: **Kai Riedmiller**

Heidelberg Institute for Theoretical Studies, Molecular Biomechanics, Heidelberg, Germany

Co-author/s: Frauke Gräter

Forces in collagen can lead to homolytic bond breakage, and thus radical formation. Previous ESR experiments have shown that those radicals often end up at dihydroxy-phenylalanine (DOPA) groups, but the exact reaction pathway through collagen is unknown. In this work, we want to examine the possible reactions the radical can undergo before ending up at DOPA. Besides hydrolysis, hydrogen atom transfer (HAT) is the most common type of reaction expected and is the focus of this work. To model the reaction pathway, graph neural networks are employed in order to predict activation energy barriers. For training the networks, training sets of structures just before a HAT reaction together with their associated energy barrier are crafted and used in a supervised learning scheme. The energy barriers are obtained using density functional theory (DFT) on structures along an estimated reaction coordinate. To correct this estimated reaction coordinate, DFT optimized structures are calculated on a subset of systems. These make up an additional, higher quality dataset, which is used in a transfer learning scheme together with the former dataset.

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Poster #231 **on-site**

The Mechanism of Sodium Binding to SERT - In Silico Investigation

Presenting author: **Daniel Szöllösi**

Max Planck Institute for Multidisciplinary Sciences, Department of Theoretical and Computational Biophysics, Göttingen, Germany

Co-author/s: Thomas Stockner

The serotonin transporter (SERT) terminates neurotransmission by transporting serotonin from the synapse into the pre-synaptic nerve terminal. Altered SERT function leads to several neurological diseases including depression, anxiety, mood disorders and attention deficit hyperactivity disorders (ADHD). Accordingly, SERT is the target for pharmacological treatment. Moreover, multiple recreational drugs also interfere with normal SERT function. Transport of serotonin is energized by the electrochemical gradient of sodium across the cell membrane. We used extensive molecular dynamics simulations to investigate the process of sodium binding to SERT, the first step in the transport cycle. Comparing data from 51 independent simulations, we find a remarkably well-defined path for sodium entry and could identify two transient binding sites, while binding kinetics that are comparable to experimental data. We find that the electric field generated by the protein attracts the sodium ions and directs them towards the respective binding sites. Importantly, structure and dynamics of the sodium binding sites indicate that sodium binding is accompanied by an induced fit mechanism that stabilizes the outward-open conformation. The loss of entropy due to conformational stabilization is compensated by the energetically favorable binding of sodium.

Poster #236 **on-site**

Molecular Dynamic Simulations of Hydrophobins: Pure-Protein Bilayers and Lipid-Protein Interactions

Presenting author: **Leonhard Starke**

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Co-author/s: Jochen S. Hub

Hydrophobins are a family of proteins characterized by a large exposed hydrophobic region, rendering them highly amphiphilic. Class II hydrophobins such as HFBI self-assemble into monolayers at water-air or water-oil interfaces, revealing long-range ordered hexagonal 'honeycomb' structures [1]. This property allows for the preparation of pure-protein bilayers and vesicles [2] with unexpectedly low permeability for water and ions. To provide a molecular explanation for these properties, we carried out atomistic and coarse grained molecular dynamics (MD) simulations of HFBI bilayers. Our results indicate that the proteins have to rearrange upon monolayer contact in order to form a stable dense bilayer.

In contact with lipid bilayers, hydrophobins were found to modulate the stability of the membrane in electroporation experiments. Coarse-grained simulations show that the proteins aggregate inside the pore and bind to the exposed hydrophobic membrane core, therefore leading to the observed stabilisation.

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Poster #264 **online**

Interaction of Quinone-Based Compounds with Mitochondrial Respiratory Complex I: A Molecular Dynamics Study

Presenting author: **Oleksii Zdorevskyi**

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Co-author/s: Hideto Miyoshi, Vivek Sharma

Mitochondrial respiratory complex I (NADH: quinone oxidoreductase) is the key enzyme in the electron transport chain and energy metabolism of a living cell. Despite the diversity of recent cryo-EM structures of complex I, its biological function at the molecular scale still remains unrevealed [1]. In the present study, we performed fully atomistic molecular dynamics simulations on a set of latest high-resolution structures of mitochondrial complex I from Ovis Aries [2]. We studied the interaction of substrate quinone (Q) and quinone-type ligands modelled at the distinct binding sites of the Q tunnel. The protein dynamics was investigated on microseconds time scales with different system sizes and several types of explicit solvent.

We have found that certain quinone analogues are more likely to move deeper into the binding cavity, whereas others prefer binding at the tunnel entrance. Moreover, the ligand behaviour in the Q tunnel is found to be coupled with the conformational changes in conserved protein loops. The protein-Q interactions identified from MD data are in partial agreement with photoaffinity labelling studies. The obtained results shed light on the possible existence of the alternative quinone reduction pathways in mitochondrial complex I.

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Poster #267 **on-site**

Mechanism by which a Cyclic-Nucleotide Gated Ion Channel Discriminates between Nucleotides Revealed by AFM Force Spectroscopy and Molecular Dynamics Simulations

Presenting author: **Emmi Pohjolainen**

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Co-author/s: Yangang Pan, Philipp Schmidpeter, Andrea C. Vaiana, Helmut Grubmüller, Crina M. Nimigean, Simon Scheuring

Cyclic nucleotide (cN) gated ion channels such as the SthK channel are crucial in many physiological processes. Strangely, and despite their chemical similarity, cAMP acts as an activator while cGMP as an inhibitor of the SthK channel. We combined atomic force microscopy (AFM) and molecular dynamics (MD) simulations to investigate the mechanism of cyclic nucleotide binding domain (CNBD) discrimination between cAMP and cGMP. While short contact time AFM measurements revealed similar binding strengths of cAMP and cGMP, from longer contact times results suggest that ligand detection originates from the difference in binding modes of cAMP and cGMP. To gain atomistic insight into the discrimination mechanism, we performed force probe unbinding MD simulations of cAMP and cGMP bound CNBD at various loading rates. Dynamic force spectra computed from the MD trajectories agree with the experiments and thus serve as a validation of the simulations. To test whether ligand selectivity can be attributed to the difference in binding modes between cAMP and cGMP, we first compared hydrogen bond interactions and their strengths along the unbinding pathways. We find differences between both the hydrogen bonding patterns of the two ligands and their lifetimes along the pathways with cAMP showing longer lifetimes than cGMP. Finally, we investigated a proposed conformational change of CNBD binding pocket closing induced by cAMP binding by computing free energy profiles for opening of the binding pocket in presence of cAMP and of cGMP. Overall, the simulations suggest that while both cAMP and cGMP are able to bind to the CNBD, the activated structure is only induced by cAMP binding.

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Poster #268 **online**

Full-Atom Model of the Activated Toll-Like Receptor 4 Dimer in a Membrane Environment

Presenting author: **Alejandra Matamoros-Recio**

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Co-author/s: Juan Felipe Franco-Gonzalez, Sonsoles Martín-Santamaría

Toll-like receptor 4 (TLR4) activates innate immunity by recognizing lipopolysaccharide (LPS) from the outer membrane of Gram-negative bacteria. TLR4 activation is associated with certain autoimmune diseases, noninfectious inflammatory disorders, and neuropathic pain.[1]

Structural studies deepening into the TLR4 activation are scarce because of the high complexity of the receptor. We have modeled by all-atom MD simulations, the structural assembly of plausible activated full-length TLR4 models embedded into a realistic plasma membrane, providing an analysis at both, molecular and thermodynamic levels of the TLR4 assembly and its biological activity.[1] Our studies give functional and structural insights into the transmembrane domain behavior in different membrane environments, the ectodomain bouncing movement, and the dimerization patterns of the intracellular domain. Our work provides TLR4 models as reasonable 3D structures for the TLR4 architecture accounting for the active (agonist) state of the receptor and pointing to a signal transduction mechanism across the cell membrane.

In addition, we have addressed the characterization of the recognition processes of TLR4 modulators by computational tools, and have proposed a mechanism for their biological activity.[2,3] Our studies unveil relevant molecular aspects involved in the TLR4 innate immune pathways and will promote the discovery of new TLR4 modulators and probes.

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Poster #271 **online**

In Silico Design of Cyclic Peptide Binders Targeting Protein-Protein Interfaces

Presenting author: **Brianda Paola Lopez Santini**

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Co-author/s: Martin Zacharias

Rational design of specific inhibitors of protein-protein interactions is desirable for drug design to control cellular signal transduction and for studying protein-protein interaction networks. We have developed a rapid computational approach (cPEPmatch) to rationally design cyclic peptides that potentially bind to desired motifs of the interface of protein-protein complexes by backbone structure matching. The methodology is based on comparing the protein backbone structure of short peptide segments (epitopes) at the protein-protein interface with a collection of cyclic peptide backbone structures. A cyclic peptide that matches the backbone structure of the segment is used as a template for a binder by adapting the amino acid side chains to the side chains found in the target complex.

Poster #282 **online**

Binding Mode Characterization of PfFNT Inhibitors through Docking and Molecular Dynamics Simulations

Presenting author: **Alejandro Martínez-León**

Saarland University, Department of Theoretical Physics, Computational Biophysics Group, Saarbrücken, Germany

Co-author/s: Jochen S. Hub

Malaria is a key threat to public health worldwide. Recently, Plasmodium-falciparum formate-nitrite-transporter (PfFNT) has been identified as the malaria parasite's lactate transporter and as a novel drug target[1]. A few putative inhibitors for PfFNT have been identified[2]. However, their mechanism of binding and inhibition is not well understood. Here, we used molecular dynamics simulation to study the function and inhibition of PfFNT at an atomic level. The ligands MMV007839 and BH267.meta have been identified as potential inhibitors. For these ligands, we derived new parameters based on GAFF2 force field. To do this, we used the HTMD Parameterize tool[3] complemented with Stochastic Conformational Analysis at the semi-empirical level with ab initio refinement. The new parameters reproduce the dihedral potentials of these ligands at the DF-MP2-aug-cc-pVTZ level of theory. This is a remarkable improvement relative to initial GAFF2 parameters. In silico, we docked the ligands into the putative binding site in the PfFNT structure. The binding of these ligands show stability over the studied time range. We have tested different flavors of parameters for Umbrella simulations; however the convergence is still a term of concern. Improvements on the equlibration phase, restrictions on the sampling space, and/or the coupling with other sampling techniques might enhance the convergence of our system. All our work has been highly automated via a Python module, to render the setup transferable to similar systems (https://gitlab.com/md_tools/mdynamic). Also a Python module for conformational analysis of small molecules has been developed (https://gitlab.com/md_tools/aleimi).

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Poster #286 **on-site**

Allostery in Nonequilibrium Simulations

Presenting author: **Ahmed Ali**

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Co-author/s: Adnan Gulzar, Steffen Wolf, Gerhard Stock

Allostery is an essential process for protein regulation. It happens by triggering the protein at site A, causing change in the binding affinity at remote site B. Although investigating this phenomenon in proteins may be weary, due to a large number of residues and changes in the protein, PDZ domains are considered to be a perfect model to study allostery, due to their small size and their possession of the 'allosteric effect'. By using a photoswitch, we perform nonequilibrium photoswitching simulations, by mimicking the initial cis to trans photoisomerization of the azobenzene photoswitch via a potential-energy surface switching method, consequently, we can imitate the allosteric process and observe it in real-time. This was done by photoswitching the peptide ligand in PDZ2, which changed the binding affinity between the peptide and the protein. For PDZ3, perturbing α3 helix changes the binding affinity of the ligand.

Moreover, the single PDZ domains did not show many changes in contacts, thus, the PDZ12 tandem become an interest due to its unique structure, it consists of two PDZ domains (PDZ1 and PDZ2) connected by a loop. It was reported that the PDZ2 domain presence stabilizes PDZ1 and its binding site through salt bridges, and by breaking these interactions between the two domains, PDZ1 becomes unstable and the ligand starts to unbind. This is considered to be a new approach to tackle the allosteric process since it is a chemically induced method.

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Poster #292 **online**

High Performance Computing for Elucidation of the Mechanism of Mutant IDH1 Induced Cancer

Presenting author: **Bharath Raghavan**

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Co-author/s: Paolo Carloni, Marco De Vivo

Specific mutations on the human Isocitrate Dehydrogenase 1 (IDH1) enzyme have been associated with cancers like Glioma and AML. These variants (which include R132H, R100A/Q, Y139D) increase the production of 2-hydroxy glutarate, leading to increased stemness of brain cells and inhibition of DNA methylases [Dang et al. 2009]. Understanding the enzymatic mechanism of wild-type and mutant enzymes may advance drug design against this important target by designing transition state analogs. In this project, we use high performance computational methods to study the reaction mechanism and design transition state analogues that could act as inhibitors. So far, we have performed a structural prediction of the Michaelis complexes of the reactions of wild type and R132H-IDH1, using molecular dynamics. This constitutes the starting point for QM/MM simulations of the reactions. We will use a newly developed, massively scalable QM/MM interface [Bolnykh et al. 2009], developed in Juelich in collaboration with several other European research centers. This will be the first application of this code to enzymatic reactions, and one the first dynamic QM/MM simulation of enzymes performed at the density functional level theory. This will lead to a better understanding of the mechanism of the disease, and allow for the scientific design of more potent drug candidates. This present an opportunity to utilize cutting-edge high-performance computing methods to solve problems in neuromedicine, and provide a blueprint for streamlined development of inhibitor candidates. This project is funded by the Helmholtz European Partnering project between Forschungszentrum Juelich and the Italian Institute of Technology, Genoa, Italy.

Poster #294 **on-site**

Computational Studies of Confinement-Controlled Chemistry in Supramolecular Cages

Presenting author: **Gers Tusha**

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Co-author/s: Lars Schäfer

Confinement-controlled chemistry deals with reactivity within nano-sized spaces. Supramolecular cages are emerging as an interesting source of molecular confinement, giving rise to a different reactivity with respect to the widely explored chemistry in bulk solvent.

The system under investigation is a host-guest complex. The host, a neutral self-assembled supramolecular cage, is designed to bind the anionic leaving group of the guest molecule. The goal, in order to gain insights on the structure-dynamics-property relationships and the reactivity within the nano-confined environment, is to firstly explore the energy landscape of the host-guest complex. In order to do so, a synergistic interplay between Quantum Chemistry (QC) calculations and Molecular Dynamics (MD) simulations is employed.

General Amber Force Field (GAFF) has been complemented through QC calculations at the Density Functional Theory (DFT) level in order to model the system of interest in the Molecular Mechanics (MM) framework. The binding/unbinding events have been studied through extensive and unbiased MD simulations. The conformational space and the underlying interactions of the complex have been analysed.

Poster #297 **on-site**

Log-Periodic Oscillations in Proteins

Presenting author: **Emanuel Dorbath**

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Co-author/s: Gerhard Stock, Steffen Wolf

Processes on multiple time scales are observed in several fields of science, particularly in biomolecular systems as proteins. These can range from picoseconds (fast bond vibrations) over nanoseconds (local conformational transitions) up to multiple microseconds (conformational restructuring of the whole system). For systems with a hierarchical free energy landscape, the time scales are present as logarithmic oscillations as seen in earthquakes, financial crashes and biomolecular systems. From the hierarchical landscape these log-oscillations arise as a direct result of a discrete scale invariance of the system which also gives rise to a power-law. This results in multiple relaxation times extending over several magnitudes of order.

An analysis is presented to derive the respective time scales using the logarithmic oscillations. For this two systems are studied: an artificial 1-dimensional hierarchical potential as proof of principle and the α-aminoisobutyric acid Aib9 whose hierarchical structure and relaxation times were studied in previous works. Aib9 is a peptide with two stable conformations being a left- and right-handed helix as well as multiple metastable states in between which must be passed over.

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Poster #301 **online**

Pre-Exascale Computing of Protein-Ligand Binding Free Energies with Open Source Software for Drug Design

Presenting author: **Vytautas Gapsys**

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Co-author/s: David F. Hahn, Gary Tresadern, David L. Mobley, Markus Rampp, Bert L. de Groot

Nowadays drug design projects benefit from highly accurate protein-ligand binding free energy predictions based on molecular dynamics simulations. While such calculations have been computationally expensive in the past, we now demonstrate that workflows built on open source software packages can efficiently leverage pre-exascale compute resources to screen hundreds of compounds in a matter of days. I will report the results of free energy calculations on a large set of pharmaceutically relevant targets assembled from industrial drug discovery projects.

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Poster #302 **on-site**

Effects of Cryo-EM Cooling on Structural Ensembles

Presenting author: **Lars V Bock**

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Co-author/s: Helmut Grubmüller

Structure determination by cryo electron microscopy (cryo-EM) provides information on structural heterogeneity and ensembles at atomic resolution. To obtain cryo-EM images of macromolecules, the samples are first rapidly cooled down to cryogenic temperatures. To what extent the structural ensemble is perturbed during cooling is currently unknown. Here, to quantify the effects of cooling, we combined continuum model calculations of the temperature drop, molecular dynamics simulations of a ribosome complex before and during cooling with kinetic models. Our results suggest that three effects markedly contribute to the narrowing of the structural ensembles: thermal contraction, reduced thermal motion within local potential wells, and the equilibration into lower free-energy conformations by overcoming separating free-energy barriers. During cooling, barrier heights below 10 kJ/mol were found to be overcome, which is expected to reduce B-factors in ensembles imaged by cryo-EM. Our approach now enables the quantification of the heterogeneity of room-temperature ensembles from cryo-EM structures.

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Poster #312 **online**

Protein Vibrations and their Localization Properties: A Numerical Scaling Analysis

Presenting author: **Felix Guischard**

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Co-author/s: Jetmir Haxhija, Jan Kaiser, Thorsten Koslowski

Using a classical force field, we investigate the localization properties of protein normal modes. For a set of eighteen proteins that cover five classes of increasing size, we compute the participation ratio as a measure of the spatial extent of protein vibrations. In this scaling analysis, we find extended low-frequency far-infrared and Terahertz modes, in contrast to localized high-frequency near-infrared vibrations. These regimes are separated by a broad crossover around a wave number of 260 cm-1. Biophysical and biochemical implications are discussed, and the vibrational localization properties are compared to those of amorphous solids.

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Poster #320 **on-site**

Modeling Protein Ensembles with Doubly Intractable Distributions

Presenting author: **Benjamin Eltzner**

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Co-author/s:

Molecular dynamics is an important tool to model and understand protein dynamics. However, in some cases properties measured from a protein ensemble, like atom distances, are not correctly recovered in simulations. To remedy this problem, ensemble refinement methods have been developed and Bayesian Monte Carlo methods have been applied. We approach the problem from the maximum entropy point of view. The problem then presents as doubly intractable and thus requires sophisticated two-step Monte Carlo methods. This approach goes beyond typical ensemble refinement approaches by providing an energy refinement and variance estimates for the energy parameters.

Poster #327 **on-site**

MD-Based Approach to Study Activation of the Mechanosensitive Ion Channel MscL in Response to Various Stimuli

Presenting author: **Olga Rogacheva**

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Co-author/s: Tiago Costa, Andreas J.W. Hartel, Carsten Kutzner, Wojciech Kopec

The Large Conductance Mechanosensitive Ion Channel (MscL) is a bacterial channel that senses membrane tension upon osmotic shock. Specifically, the application of membrane tension activates the channel, leading to a major conformational change that results in a channel opening. Consequently, ions leave the cell through open MscL, preventing cell lysis. Although membrane tension is the most common way to activate MscL, other factors, such as membrane lipid composition, point mutations, and ultrasound stimulation also lead to the channel opening. Interestingly, it is still unclear whether channel activation under these stimuli shares the same intermediate and final states with the tension-induced activation, or passes through other states.

Here, we compared McsL activation in response to membrane tension, focused ultrasound waves and lysolipids addition to both or single leaflets. To take advantages from long-timescale simulation (> 2 μs), we used three levels of coarse graining: 1) full-atomic models (charmm36m and slipids/amber14 force fields), 2) virtual sites based models with the same force fields as in the full-atomic model and increased time step of 4 fs, and 3) coarse-grained Martini models. The pathways of MscL gating and the applicability of full-atomic and coarse-grained models for studying MscL activation are discussed.

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Poster #329 **on-site**

Uncertainty in Markov State Models of Small Macromolecules

Presenting author: **Nicolai Kozlowski**

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Co-author/s: Helmut Grubmüller

Markov State Models (MSMs) are a tool to describe and analyse protein dynamics. They are useful in particular to determine characteristic timescales of protein motion. For larger biomolecules such as proteins it is challenging to obtain sufficient sampling for the timescales to converge, which is thus a frequent concern. To estimate uncertainty of MSM timescales due to insufficient sampling, a Bayesian sampling method is commonly used instead of cross-validation. There are, however, also several other sources of uncertainty, such as choice of lag time and the number of dimensions in the dimension reduction preprocessing step (e.g. time-lagged independent component analysis), the number of Markov states, or choice of the MSM lag time. To quantify and rank the uncertainties of MSM timescales induced by these choices, we constructed MSMs for four small macromolecules: human Pin1 WW-domain (PDB code: 2f21, 35 residues), the Homeodomain of mouse HNF 6 (1s7e, 50 res.), the protein Fasciculin 1 (1fas, 61 res.), and the XPC-binding domain of protein hHR23B (1pve, 72 res.). For every macromolecule, several parameter combinations and amounts of sampling were considered. Using cross-validation, we found that the largest uncertainty is due to insufficient sampling, and somewhat smaller uncertainties arise from changing parameters or the random seed. The Bayesian sampling method systematically underestimates the uncertainties.

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Poster #330 **online**

Insights into the Operation Mode of ABCE1 via Markov Models

Presenting author: **Malte Schäffner**

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Co-author/s: Helmut Grubmüller

ABCE1 is a remarkable structural exception of the ubiquitous ATP Binding Cassette (ABC) superfamily. Unlike almost all other members, ABCE1 lacks transmembrane domains and comprises only the 'core engine' of all ABC proteins, and therefore is an ideal prototype for studying the mechanism of ABC proteins in general. Each of its two homologous nucleotide binding domains (NBD) contains one nucleotide binding site, which can be in an open and a closed state. Despite this near symmetry, and quite unexpectedly, the kinetics has been found quite asymmetric: Whereas a E238Q point mutant that impairs ATP hydrolysis in one of the two binding sites reduced the overall turnover rate of the enzyme by a factor of two, as one might expect, a E485Q point mutant that impairs the other site, staggeringly, shows a so far unexplained ten-fold increase.

To address this issue, we used Markov models to study how such asymmetry can arise. Specifically we asked if previously proposed long range couplings or allosteric interactions between the two binding sites are really required to explain this observation. Indeed, using a Bayesian approach, we found Markov models that quantitatively match the measured kinetics as well as additional occupation data, and nevertheless did not require any coupling or allostery beyond the structure-induced property that opening and closing always involves both NBSs. The unexpected fast kinetics of the second mutant is explained in terms of dominant reaction pathways, which change drastically for the second mutant allowing circumvention of the rate-limiting step present in wild-type and first mutant. We expect that this Bayes/Markov approach can help, quite generally, to gain a systematic and quantitative understanding of enzymatic kinetics governed by coupled chemical and conformational dynamics as a basis for rational enzyme optimization.

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Poster #335 **online**

Scalable QM/MM Simulations of Biological Systems using Novel GROMACS-CP2K Interface

Presenting author: **Dmitry Morozov**

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Co-author/s: Christian Blau, Gerrit Groenhof

Simulations of chemical reactions pathways can provide an atomistic insight into many biological and chemical processes. To perform such kind of modelling in complex systems, that includes solvent and/or proteins Multi-scale Quantum Mechanics / Molecular Mechanics (QM/MM) approaches are often used. Here we introduce a whole new interface to perform QM/MM simulations in fully periodic systems using MDModule that couples GROMACS with CP2K quantum chemistry package. This enables hybrid simulations of systems in systems where chemical reactions occurs. The interface supports most of the simulations techniques available in GROMACS including: energy minimization, classical MD and enhanced sampling methods such as umbrella sampling and accelerated weight histogram method to perform scalable modelling of reactions inside biological systems.

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Poster #343 **on-site**

Fear Not Complexity: Molecular Dynamics Simulations of Pgp in a Composite Membrane Blend Reveal Functional Lipid Wedges

Presenting author: **Dario De Vecchis**

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Co-author/s: Lars Schäfer

Human P-glycoprotein (Pgp) is an ATP-binding cassette transporter which hydrolyzes ATP to energize the efflux of lipids and hydrophobic compounds throughout the plasma membrane against their concentration gradient. The protein is associated with the development of multidrug resistance, is often overexpressed in a variety of cancers and therefore target of intensive studies. Here we employ all-atom and coarse-grained molecular dynamics simulations to study Pgp conformational landscape in presence or absence of ATP. Microsecond simulations have been performed in a native-like asymmetric lipid mixture that resembles a highly specialized hepatocyte cell membrane enriched with cholesterol and sphingolipids. The study confirms the role of the nucleotide as a central hub for dimerization and reveals different lipid species wedging between the Pgp transmembrane helices and entering the main substrate cavity, suggesting their possible concerted role for an efficient substrate efflux.

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Poster #347 **on-site**

Selectivity Filter Gating in the MthK Potassium Channel and its V55E Mutant

Presenting author: **Wojciech Kopec**

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Co-author/s: Brad Rothberg, Bert L. de Groot

Potassium channels are essential proteins playing key roles in a multitude of physiological functions. These channels conduct potassium ions down their electrochemical gradient and undergo complex conformational changes between 'open', 'closed' and 'inactivated' states. The open-to-inactivated transition (C-type inactivation) is of particular interest, as it occurs at the key structural element of all potassium channels - the selectivity filter. Recent structures of different potassium channels obtained in conditions promoting C-type inactivation revealed a surprising conformational variety of inactivated filters. For example, in contrast to a well-known 'constricted' conformation seen in the prototypical bacterial channel KcsA, the voltage-gated Shaker channel adopts a 'dilated' conformation, even though the selectivity filter sequence is identical in these two channels.

Molecular Dynamics (MD) simulations allow to study ion permeation and gating transitions occurring at the selectivity filter, and are therefore an invaluable tool to gain insights into their stability and dynamics. Here, we focused on the well-studied bacterial channel MthK, which possesses a subtle selectivity filter regulation as well as undergoes C-type-like inactivation, although the inactivation mechanism is not fully understood. We introduced the KcsA-like V55E mutation in MthK, which in experiments destabilizes the open state. Surprisingly, our MD simulations reveal that both wild-type and V55E channels inactivate in a manner more comparable with Shaker and not with KcsA. The factors determining different C-type inactivation pathways will be discussed.

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Poster #358 **on-site**

Understanding Ultrafast Protein Dynamics in Crystals

Presenting author: **Lukas Ishmael Krieger**

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Co-author/s:

Since the advent of free electron lasers that emit coherent X-rays with high brilliance and pulse durations of less than 1 ps it is possible to follow structural transitions in proteins on the time scale of a few picoseconds. In my project I am investigating the ultrafast process of CO-dissociation in myoglobin induced by irradiation of a 532 nm laser beam. Experimentally the structural changes due to CO-photodissociation are followed by a X-ray beam produced at a X-ray free electron laser (XFEL) (see Schlichting et al. "Direct observation of ultrafast collective motions in CO myoglobin upon ligand dissociation", Science 2016). A remaining question is in which matter the higher order structure of protein crystals can influence the dynamics of picosecond during reactions inside the molecule. Based on QM/MM simulations I will model the structural change of the heme group and a nearby histidine residue during the process of photodissociation. It turns out that the transition from an iron six-coordinated singlet to a five-coordinated quintuplet state involves a movement of the iron and proximal histidine away from the heme plane and a slight doming of the heme itself that was also reported by Schlichting and that we hope to reproduce by QM/MM simulations.

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Poster #359 **on-site**

Experiment-Guided Molecular Simulations Reveal the Heterogeneous Ensemble of the SH2 Tandem of SHP2 Phosphatase

Presenting author: **Massimiliano Anselmi**

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Co-author/s: Jochen S. Hub

SHP2 plays an important role in upregulating cellular processes, so much that its mutations cause developmental disorders and are found in many cancer types. SHP2 is a multidomain protein, comprising two tandemly arranged SH2 domains and a catalytic PTP domain. SHP2 is activated upon binding of two linked phosphopeptides to its SH2 domains. Experiments showed that peptide orientation and spacing between binding sites are critical for the enzymatic activation. For decades, the SH2 tandem has been extensively studied to disclose the relative orientation of the two SH2 domains that effectively drives to activation. So far, crystallography has provided only contradictory results, while measures in solution resulted of difficult interpretation. By means of experiment-guided molecular simulations, we have finally revealed the heterogeneous ensemble of the SH2 tandem in solution, in agreement with the available experimental data from small-angle X-ray scattering and NMR residual dipolar couplings.

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Poster #361 **on-site**

Voltage Sensing in Protein-Conducting Channel SecYEG

Presenting author: **Ferdinand Horvath**

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Co-author/s: Thomas Renger

The bacterial channel SecYEG is responsible for translocating proteins across the plasma membrane. It resides in an energized membrane subjected to the proton motive force (PMF). Experimental reports have shown that the PMF's electrostatic component allows SecYEG to remain impermeable to ions. When the absolute value of the transmembrane electrostatic potential drops below a certain threshold, however, the channel becomes leaky. The precise mechanism behind this voltage-dependent ion channel activity is still unclear. We employ molecular dynamics simulations to study SecYEG's mechanical response to transmembrane voltages. Although electric fields induce only minute displacements of secondary structure elements within the channel, detailed analysis of intramolecular forces reveals a complex pattern of voltage-dependent stress inside the channel. Using force distribution analysis, we discern voltage-sensitive elements in the channel and highlight networks of interacting residues that constrict the channel pore in the presence of electric fields. We find that, depending on the sign of the transmembrane potential, either helices TM 5 and 7 or TM2 and the plug domain are the most voltage-sensitive elements of the channel.

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Poster #363 **on-site**

Elongation Factor G and Bacterial Resistance to Aminoglycosides

Presenting author: **Sara Gabrielli**

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Co-author/s: Helmut Grubmüller, Lars Bock

During translation, when the ribosome moves along the mRNA, the tRNAs bound to the ribosome translocate between different binding sites. Elongation Factor G (EF-G) uses the energy from GTP hydrolysis to accelerate tRNA translocation. Aminoglycosides are antibiotics which induce the addition of incorrect amino acids to the nascent peptide chain. Interestingly, several disease-causing bacteria that contain mutants of EF-G display resistance towards aminoglycosides, but the resistance mechanism is not yet clear. Since EF- G undergoes conformational changes during translocation and mutations were shown to affect translocation rates, we hypothesize that perturbations of the EF-G dynamics and energetics caused by the mutations play a fundamental role. Unexpectedly, the EF-G mutations identified in resistant bacteria are distributed over all EF-G domains, in internal and in exposed regions. The more internal locations suggest internal EF-G dynamics, independent of the interactions with the ribosome, might contribute to the resistance mechanism.

Here we use extensive all-atom Molecular Dynamics simulations of wild-type and mutated EF-G from several organisms in solution to investigate the effect of these mutations on the internal dynamics and energetics of EF-G.

Principal Component Analysis of EF-G trajectories has revealed that the most pronounced inter-domain motion is the rotation of domains IV-V relative to domains I-III. Interestingly, for most of the mutants, this rotation is restricted compared to wild-type EF-G. Potentials of mean force calculated along the first principal component, display a free-energy minimum that is accessed by wild-type EF-G and not by some of the mutants. Given the importance for translocation of the interactions between EF-G domain IV, ribosome and A-site tRNA, we expect free-energy changes of domain IV rotation to influence the protein's function and provide a possible explanation for the resistance mechanism.

Poster #368 **on-site**

Computational Study of the Channelrhodopsin Chrimson Wild-Type and Mutants

Presenting author: **Katharina Spies**

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Co-author/s: Beatrix M. Bold, Marcus Elstner

The channelrhodopsin Chrimson is the most red shifted cation channel currently known and thus of great importance in optogenetics studies as red light has low phototoxicity and penetrates deep into biological tissue.[1, 2] In optogenetics, neuronal activity is influenced by de- or hyperpolarization of selected cells using light-gated ion channels.[3]

Like all microbial rhodopsins, Chrimson has seven transmembrane α-helices and the chromophore retinal.[4] The protein's active site consists of RSB+ and two counterions (E165 and D295) with a unique protonation state in comparison to other channelrhodopsins since one of them is protonated.[2]

We present a computational study to investigate the ground state active site structure of Chrimson by using quantum mechanics/molecular mechanics (QM/MM) simulations of the wild type and different mutants. The excitation energies of a large ensemble of QM/MM trajectory snapshots were calculated with LC-TD-DFTB, LC-TD-DFT and SORCI.[5, 6] The computed results are compared to experimental results. The investigation of the protonation state of the counterions leads to the conclusion that the proton is shared by both of them. As well, the protonation states of titrable amino acids in the putative ion pore were determined. In addition, the calculations of the absorption spectra of mutants of residues in and near the active site (E165Q, D295N, S169A and S169D) confirm experimental findings and therefore facilitate a detailed structural analysis of the residues responsible for the color tuning in Chrimson.

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Poster #369 **online**

Langevin Models from Constrained MD Simulations

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Co-author/s: Steffen Wolf, Gerhard Stock

The intricate motion of biomolecular systems is often described by Langevin models, reducing their complexity to a set of only few relevant collective variables and viewing them as moving in a free energy landscape subject to friction and random noise. For large-scale proteins, with biologically relevant timescales ranging from few femtoseconds to multiple seconds, building those models from the microscopic level is only possible with biased simulations, which enforce rare transitions over high energy barriers.

Here, we study dynamics restored from Targeted MD simulations, constraining a reaction coordinate to move from one to another state.[1] If the distribution of the work is Gaussian, it can be shown that a Langevin model is valid. The free energy landscape in the whole collective variable space can be recovered by use of generalized Jarzynski's equality, revealing distinct reaction pathways.[2] The position dependent memory kernel or friction can be calculated through the constraint force auto-correlation.[3] Taking into account the influence of the constraint and pulling rate, we study the friction profile for various molecular systems.

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Poster #375 **on-site**

Coarse-Grained Modeling of Salbutamol and Salmeterol Binding to Beta 2-Adrenergic Receptor

Presenting author: **Cristina Gil Herrero**

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Co-author/s: Sebastian Thallmair

The beta 2-adrenergic receptor (B2AR) belongs to the family of G protein-coupled receptors, one of the major drug targets. G protein-coupled receptors are integral membrane proteins that convert external signals into intracellular responses. Two already known drugs employed in the treatment of several respiratory diseases are salmeterol and salbutamol. They show a high affinity to B2AR, however, their binding pathways have not yet been fully characterized.

Along this project we will shed light on the binding process by means of coarse-grained molecular dynamics simulations using the Martini 3.0 force field. This methodology enables us to study the binding pathway of both drugs in an unbiased way.

First, we parametrized the new ligands and the target protein according to the Martini 3.0 model. The defined parameters were in good agreement with all-atom simulations and experimental properties. In addition, the analysis of the ligands' behaviour within different membrane compositions provided fundamental details such as the high membrane affinity of salmeterol indicated by its longer residence time in the membrane compared to salbutamol. The placement of the ligands in their known binding site showed residence times expected for their high affinity to B2AR. Afterwards, a system composed of B2AR embedded in a membrane including multiple ligands in the water phase was simulated. Based on the binding events observed along the different simulation replicas, we will analyze the ligand hot spots on the B2AR surface as well as their binding pathways and affinities.

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Poster #377 **on-site**

A Proposed Mechanism for Vibrio Export Monitoring Polypeptide Folding in the Ribosome Exit Tunnel

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Co-author/s: Michal H. Kolar, Lars V. Bock, John D. Kunkel, Sara M. Vaiana, Helmut Grubmüller

The ribosome is a fundamental biomolecular complex that produces proteins in cells. The nascent chains of the new synthesized proteins are produced deep within the ribosome at the peptidyl-transferase center (PTC) and pass though the ribosomal exit tunnel before they fold into their functional conformations. The Vibrio export monitoring polypeptide (VemP) is a mechano-sensitive regulatory peptide that folds into a helix-loop-helix structure in the ribosome tunnel near the PTC, which causes elongation arrest. Unless the ribosome is rescued by sodium-depend membrane transporters, this elongation arrest triggers an alternative gene expression for proton-driven membrane transport, and adapts Vibrio to a low-salinity environment.

Here, we studied the driving forces of the VemP helix formation by combining all-atom molecular dynamics (MD) simulations of VemP constructs both in the ribosome and in water with circular dichroism (CD) spectroscopy measurements in trifluorethanol/water mixtures. We show that the helix propensity of VemP is low in pure water, but increases in a more hydrophobic solvent environment. This finding combined with our MD simulations suggests that VemP helix formation largely is driven by the solvent environment of the tunnel, and specific interactions with the tunnel walls stabilize its structure. Further, the simulations of VemP in the ribosome also suggest that the loop structure in VemP acts as an anchor, which slows down the peptides progression in the tunnel, enabling -helix formation, and the consequent elongation arrest.

Poster #383 **online**

Modeling Charge Transport in Organic Semiconductors

Presenting author: **Sara Roostaei**

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Co-author/s: Weiwei Xie, Marcus Elstner

Trajectory surface hopping (TSH) method has been applied to study charge/exciton transport process in organic semiconductors (OSCs). In the present study, we systematically examine the performance of two approximations in the fewest switched surface hopping (FSSH) simulations for charge transport (CT) in several representative OSCs. These approximations include (i) the substitution of the nuclear velocity scaling along nonadiabatic coupling vector (NCV) by rescaling the hopping probability with the Boltzmann factor (Boltzmann correction(BC)) and (ii) a phenomenological approach to treat the quantum feedback from electronic system to nuclear system (implicit charge relaxation (IR)) in the OSCs. A key parameter determining charge carrier mobility is the reorganization energy, which is very dependent on DFT functionals. By employing IR approximation, the FSSH method allows to investigate the effect of the reorganization energies obtained by different DFT functionals on CT in OSCs. First, wefind the charge mobilities computed by FSSH-BC-IR are in very good agreements with the mobilities obtained by standard FSSH simulations with explicit charge relaxation (FSSH-ER). Then we perform the FSSH-BC-IR simulations using reorganization energies obtained by B3LYP and !B97XD functionals, respectively, as input parameters for IR approximation. In comparison to the experiments, FSSH-BC-IR using !B97XD reorganization energy underestimates mobilities in the low-coupling regime, which may be due to the lack of nuclear quantum effects (e.g., zero point energy (ZPE)) in the simulations. The mobilities obtained by FSSH-BC-IR using B3LYP reorganization energy functional agree well with experimental values in three orders of magnitude. The accident agreements may be the consequence of the underestimation of the reorganization energy by B3LYP functional, which compensates the nuclear ZPE loss in the simulations.

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Poster #390 **on-site**

Towards Understanding the Functional Dynamics of ACP Mediated Substrate Transport in the Fungal Fatty Acid Synthase

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Co-author/s: Helmut Grubmüller

Fatty acid biosynthesis is a central pillar of metabolism providing essential molecules for energy storage, signal transduction and cell wall integrity. In eukaryotes the multiple enzymes required for the synthesis of fatty acids are combined in large multifunctional enzyme complexes. The nascent fatty acid is shuttled between enzymatic domains by an integral acyl carrier protein (ACP). This transfer process is assumed to be stochastic, regulated primarily by steric occlusion and the spatial organization of active sites within the multienzyme complex. In addition, recent studies have identified a regulatory subunit, which can alter the enzymatic activity of the fungal fatty acid synthase (FAS). Cryo-electron microscopy shows that this change in activity is concomitant with a conformations rearrangement of the ACP domain. Yet it is unclear how the presence of this subunit alters the dynamics of substrate transport.

Here we show the effect of the regulatory subunit on the dynamics of ACP following initiation of fatty acid biosynthesis. To this end we modeled the 2.5 MD yeast FAS based on cryo-electron microscopy structures. Although structures of the FAS exist, important functional regions, such as the intrinsically disordered linkers connecting ACP with the FAS can not be resolved experimentally. These linker regions were modeled into the complete complex following extensive molecular dynamics simulations. Consequently we investigated the dynamics of ACP in the presence and absence of the regulatory subunit to correlate changes in the dynamics of the carrier domain with changes in enzymatic activity. Overall our work provides insights into carrier mediated transport in multifunctional enzyme complexes. This process is pivotal to the function of the FAS and presents a key component in optimizing the enzyme for biotechnological application.

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Poster #393 **online**

Identification and Inhibition of the Allosteric site of SARS-CoV-2 NSP10/NSP16 Methyltransferase

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Co-author/s: Shah Faisal, Mohnad Abdalla

SARS-CoV-2 has ravaged the health of millions of people globally and affected almost every sphere of life. Many efforts are being made to combat the COVID-19 pandemic's emerging and recurrent waves caused by its evolving and more infectious variants. As a result, novel and unexpected targets for SARS CoV-2 have been considered for drug discovery. 2'-O-Methyltransferase (nsp10/nsp16) is a significant and appealing target in the SARS CoV-2 life cycle because it protects viral RNA from the host degradative enzymes via a cap formation process. In this work, we propose prospective allosteric inhibitors that target the allosteric site SARS COV-2 MTase. Four drug libraries containing ~119,483 compounds were screened against the allosteric site of SARS-COV-2 MTase identified in our research. The identified best compounds exhibited robust molecular interactions and alloscore-score rankings with the allosteric site of SARS-COV-2 MTase. Moreover, to further assess the dynamic stability of these compounds (CHEMBL2229121, ZINC000009464451, SPECS AK-91811684151, NCI-ID=715319) a 100 ns MD simulation along with its apo-form were performed that provided insights on the dynamic nature of these allosteric inhibitors at the allosteric site of the SARS COV-2 MTase. Additionally, investigations of MM-GBSA relative binding free energies revealed a good perspective for these allosteric inhibitor/enzyme complexes, indicating their robust antagonistic action on SARS-COV-2 (nsp10/nsp16) methyltransferase. We conclude that these allosteric repressive agents should be further evaluated through investigational assessments in order to combat the recurring spread of COVID-19.

Poster #401 **online**

Effect of Transmembrane Domains on the Free Energy of Stalk Nucleation during Membrane Fusion

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Co-author/s: Chetan S. Poojari, Jochen S. Hub

The nucleation of the stalk is the first step in membrane fusion. The overall fusion process including the stalk formation is facilitated by fusion proteins anchored in the membrane by transmembrane domains (TMDs). Although TMDs of fusion proteins have been suggested to play an active role during fusion, little quantitative or mechanistic understanding of putative TMD effects has evolved. We used molecular dynamics simulations to analyze the influence of TMDs of the SNARE complex and of viral fusion proteins on the free energy of stalk formation. The stalk free energy was computed highly efficiently via potential of mean force (PMF) calculations along a newly designed reaction coordinate together with the Martini coarse-grained force field [1][2]. The results reveal a decrease in both, the free energy barrier of stalk nucleation as well as the free energy of the final stalk structure, when TMDs are present in the membrane. However, the observed TMD effect strongly depends on the lipid composition and on the hydrophobic mismatch between the TMD and membrane core, as well as on the number of TMDs inserted in the membrane. We could explain the free energy decrease upon insertion of TMDs with an increased disorder in the lipid packing quantified by the order parameter.

[1] Jochen S. Hub and Neha Awasthi. Probing a Continuous Polar Defect: A Reaction Coordinate for Pore Formation in Lipid Membranes. Journal of Chemical Theory and Computation (2017).

[2] Chetan S .Poojari, Katharina C. Scherer, and Jochen S. Hub. Free energies of membrane stalk formation from a lipidomics perspective. Nature Communications (2021).

Poster #402 **online**

Prolyl Cis-trans Isomerization Investigated with Advanced Hamilton Replica Exchange Molecular Dynamics

Presenting author: **Maximilian Kienlein**

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Co-author/s: Maria Reif, Martin Zacharias

Proline is the only amino acid able to adopt distinct cis-trans conformations. This intrinsically slow isomerization mechanism allows proline to act as a backbone switch, which is involved in the regulation of numerous biological processes ranging from protein folding, cell signaling cascades and ion channel gating to neurodegeneration and more.

However, not all prolines are essential for the regulation of these processes. For example, protein folding may continue at a normal rate despite having non-native conformers of many prolyl peptide bonds.

Here, we present an advanced sampling method employing Hamiltonian Replica Exchange Molecular Dynamics simulations aiming to determine the cis/trans equilibria of the different conformers via efficient and accurate free-energy calculations.

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Poster #407 **online**

Machine Learning Based Optimization for Tumor Simulations

Presenting author: **Julian Herold**

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Co-author/s: Alexander Schug, Eric Behle, Jakob Rosenbauer, Marco Berghoff

Despite decades of substantial research, cancer remains a ubiquitous scourge in the industrialized world. Effective treatments require a thorough understanding of macroscopic cancerous tumor growth out of individual cells in the tissue and microenvironment context. Clinical imaging methods only detect late-stage macroscopic tumors and provide low resolution imaging, while many quantitative experiments focus on small clusters of cancerous cells in microscopic detail but struggle to grow full tumors in-vitro.

Here, we aim to introduce the critical scale-bridging link between both these scopes by applying machine learning to drive model building between them. We want to simulate mm-sized virtual tissues such as embryogenetic brain tissue or cancerous tumors with more than a million µm- resolved individual cells by employing highly parallelized code on a supercomputer. Machine learning will be used to combine different scales of imaging as well as clinical and qualitative measurements to drive model generation and parametrization.

The central problem lies in the comparison between experimental and simulated data. Since both simulation as well as experiments are driven by stochastic processes, one can not directly compare individual trajectories. Here I discuss how to implement machine learning methods to enable this comparison.

Poster #408 **on-site**

Free Energy Simulations of Electroporation

Presenting author: **Gari Kasparyan**

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Co-author/s: Jochen Hub

Biological cells are defined as the volume enclosed by a semi-permeable lipid membrane. Forming pores in those membranes plays a role in processes such as membrane fusion and fission, increasing the permeability of the membrane, and others. Electroporation is a method used for decades to help introduce drugs and genetic material in cells or generally as a pore forming modality. Although pores are heavily studied with a variety of methods, the free energy landscape of the initial stages of the pore formation is still not fully understood. We use molecular dynamics simulations to study the mechanisms and energetics of electroporation. We overcome the challenge of exploring the free energy landscape using umbrella sampling along a recently developed reaction coordinate[1, 2]. The potentials of mean force (PMFs) show that electric fields greatly stabilize open pores and lower the barrier for pore formation (as expected). An unexpected discovery is the way in which the pore formation energy barrier is influenced by the applied potential. As a result of that discrepancy between simulations and existing continuum models we propose a novel continuum model of electroporation. To verify our findings we compare two methods for establishing transmembrane potential in an MD simulation – external electric field and charge imbalance.

[1] J. Hub and N. Awasthi, J. Chem. Theory Comput. 2017, 13, 2352-2366

[2] J. Hub, J. Chem. Theory Comput. 2021, 17, 1229−1239

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Poster #412 **on-site**

Investigating Human Ire1α Assembly Process via Multiscale Molecular Dynamics Simulations

Presenting author: **Elena Spinetti**

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Co-author/s: Jan Stuke, Roberto Covino, Elif Karagöz

In all eukaryotes, the Unfolded Protein Response (UPR) is a molecular program that maintains the protein folding homeostasis in the endoplasmic reticulum (ER). The UPR plays a crucial role in health and disease. Stress sensors proteins on the ER membrane activate the UPR. The evolutionary most conserved sensor is the protein IRE1, which activates the UPR by forming dimers and larger assemblies. In particular, IRE1's luminal domain (LD) interacts with unfolded proteins, and these interactions promote oligomerization by an unresolved mechanism.

My work aims at elucidating the structure and assembly mechanism of large supramolecular assemblies of human IRE1. These are crucial for IRE1's functions but are not yet understood. We study this phenomenon through a multiscale approach, performing atomistic and coarse-grained (CG) molecular dynamic (MD) simulations. We carried out simulations using the coarse-grained Martini 3.0 force field, specifically implemented to reduce the previously overestimated protein-protein aggregation. We obtained encouraging results from simulations of three disordered regions: they exhibit different aggregation propensities. We analyzed the contacts from these simulations to identify possible dimer-dimer interaction interfaces.

Recently, it has been shown that some features of disordered proteins are not accurately represented in Martini 3.0 due to underestimated protein-water interactions. Therefore, we rescaled these interactions that might affect the disordered regions. This approach is yielding promising results. We plan to use these rescaled simulations to sample possible dimer-dimer interaction configurations and afterwards back map them to an atomistic representation. Furthermore, we wish to investigate the direct binding of unfolded peptides through atomistic MD simulations of the dimer.

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Poster #418 **on-site**

Insight into the Activation Mechanism of the c-Met Receptor Ectodomain from a Mechanistic Point of View

Presenting author: **Serena Maria Arghittu**

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Co-author/s: Roberto Covino, Mike Heilemann

The human tyrosine-protein kinase Met is a transmembrane receptor placed across the plasma membrane. Also called the c-Met receptor, it is involved in a crucial signalling process that regulates cell migration and replication, enabling epithelial tissue development and renewal, both in embryos and adults. In contrast to its fundamental role in cell survival, the over-expression of c-Met strongly correlates to accelerated metastatic growth in several kinds of cancers. With the aim of shading light on the information transduction process leading to these dramatic outcomes, we focused on the presumed activation mechanism of the ectodomain of the receptor. Atomistic MD simulations have been exploited to investigate the rearrangement of the ectodomain upon biding with a non-native ligand, Internalin-B (InlB). Additionally, as anomalous post-transcriptional glycosylation is also involved in oncogenesis and cancer development, we also considered the behaviour of the N-glycosylated form of the ectodomain. To perform the simulations, we produced four models based on a low-resolution crystallographic structure (PDB ID: 2UZY): the ectodomain in isolation, the complex of the ectodomain with the Internalin and the two corresponding glycosylated structures. The analysis of the obtained trajectories revealed the signalling-competent conformation assumed by the upper domains of the ectodomain while identifying the angle among them as the discriminant between signalling- and non-signalling-competent conformations. Furthermore, we observed alternating bridging interactions among the glycans, which provides insight into their role in reducing the configurational space of the isolated ectodomain. To challenge these findings we also produced two additional models: the complex of the ectodomain with a fragment of the InlB, namely InlB_241, and the isolated ectodomain with partial glycosylation. The behaviour observed for the former model confirmed our interpretation concerning the signalling-competent conformations. Similarly, even though still in a preliminary sampling stage, the partially glycosylated model highlighted the crucial role of the glycans in affecting the structure conformation.

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Poster #420 **online**

Engineering of an Organic Solvent Tolerant Esterase based on Computational Predictions

Presenting author: **Lara Scharbert**

Research Center Jülich, Institute of Biological Information Processing (IBI-7), Computational Biochemistry, Jülich, Germany

Co-author/s: Alexander Bollinger, Anna Jäckering, Jennifer Loschwitz, Stephan Thies, Karl-Erich Jaeger, and Birgit Strodel

Biocatalytic reactions in synthetic chemistry are often carried out in the presence of organic solvents to solubilize substrates or shift the reaction equilibrium towards synthesis. However, enzymes are biocatalysts evolved by nature to work in aqueous solution; hence, organic solvent tolerant enzymes are needed and understanding the molecular basis of their resistance is highly desired.

We have recently discovered the esterase PT35 which we used here as a paradigm for an organic solvent tolerant enzyme. The enzyme was active and stable (Tm 49 °C; t1/2 35 h) in the presence of 50 % acetonitrile.

Molecular dynamics (MD) simulations of PT35 and the esterase ED30, an organic solvent-sensitive structural homolog of PT35, indicated a stronger hydration shell of PT35 maintained by its distinct negative surface charge.

We developed a mutagenesis strategy based on MD simulations with the aim to strengthen the hydration shell around the enzyme by modifying its surface charge. We constructed PT35 variants with a less negative surface charge and ED30 variants with a more negative surface charge resulting in less tolerant PT35 variants (e.g. Δt1/2 -26 h) and more tolerant ED30 variants (e.g. Δt1/2 +37 h).

In conclusion, we demonstrate here that the surface charge is a major prerequisite for high tolerance of esterase PT35 towards organic solvents. Furthermore, our results suggest engineering of an enzyme's surface charge as a tool to improve its organic solvent tolerance.

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Poster #421 **on-site**

Bayesian Structure Determination from Single Molecule X-Ray Diffraction

Presenting author: **Steffen Schultze**

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Co-author/s: Helmut Grubmüller

Single molecule X-Ray diffraction experiments are a promising new method for the structure determination of biomolecules. The reconstruction of the structure from these experiments is quite challenging: Available analysis methods require at least 100 photons per image, or a very large number (e.g. 10^9) of images. We present a novel hierarchical Bayesian approach that requires fewer photons per image and, at the same time, a relatively few images. It is flexible in that many different representations of the electron density can be used, both in Fourier space and directly in real space. Using synthetic data, we demonstrated the method is able to recover the atomic structure of (fictional) 20-atom molecules using only 5000 images with on average 15 photons each, and the structure of the protein crambin at 3.8Å resolution using only 10^8 images. Scaling to larger molecules and higher resolution is work in progress.

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Poster #422 **on-site**

Evaluating Changes in Configurational Entropy with Molecular Dynamics Simulations

Presenting author: **Lauren Finn**

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Co-author/s: Leon Wehrhan, Bettina Keller

The role of dynamics in thermodynamics is deeply linked to configurational entropy, making it a key property in the characterization of molecules suitable for the rational design of biomolecules. Here, the change in configurational entropy is evaluated for the noncanonical amino acid ethylglycine upon one, two and three hydrogen-to-fluorine substitutions in the side chain using molecular dynamics simulations. Application of the quasi-harmonic approximation method yields an upper bound on the configurational entropy of these molecules. It is shown that inclusion of pairwise supra-linear corrections are necessary for even qualitative insight on the impact of fluorination on the configurational entropy. Additionally, the choice between a cartesian and an internal coordinate system for the analysis is assessed.

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Poster #424 **on-site**

A Machine Learning Implicit Solvent Approach for Molecular Dynamics

Presenting author: **Yaoyi Chen**

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Co-author/s: Andreas Krämer, Nicholas E. Charron, Brooke E. Husic, Cecilia Clementi, and Frank Noé

Implicit modeling of solvent effects is capable of speeding up molecular dynamic calculations of large biological systems, but often lack accuracy and some physical properties compared to the explicit solvent methods. Here we introduce ISSNet, a machine learning implicit solvent model to learn from explicit solvent simulation data. It leverages the multi-scale coarse graining theory and a graph neural network architecture to achieve good approximation of energetic and thermodynamic properties. When applied to simulation of test protein systems, the ISSNet models outperformed widely-used generalized Born and surface area models in reproducing the conformational distributions. The proposed method may benefit the accurate modeling of solvent effects for in silico research and biomedical applications.

Poster #426 **on-site**

Simulation of Hydrogels with Low Polymer Mass Fraction

Presenting author: **Frederick Heinz**

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Co-author/s: Bettina Keller, Jonas Proksch

The understanding of molecular dynamics for low polymer mass fraction (w<1%) hydrogels provides unique challenges for MD simulations. Since these hydrogels have mesh sizes of 30 to 200 nm, a complete simulation of a hydrogel structure is impossible with standard MD simulations and the strong reliance on correct water dynamics makes CG impossible. In the first step, we show the validation of a model for short coiled-coil peptides that reproduce experimental data and self assembles themselves into fiber strings. In a second step, we try to understand the (long-range) interactions that make low polymer mass fraction hydrogels even possible and provide the whole system with its gel-like structure.

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Poster #428

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In Silico Tumor Invasion Dynamics

Presenting author: **Eric Behle**

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Co-author/s: Julian Herold, Jakob Rosenbauer, Marco Berghoff, Alexander Schug

Cancer is one of the most complex diseases plaguing humanity, and while enormous progress has been made during decades of research, it still remains insufficiently understood. In particular, the mechanisms driving tumor invasion and metastasis are a topic of interest. Current studies deal with collective cellular behavior within tumors, such as jamming and unjamming, which respectively lead to solid and fluid tissue dynamics. Furthermore, the extracellular matrix (ECM) surrounding the tumor has recently come into focus as a driving force in facilitating invasion. To complement these experimental investigations, computational models are employed, and recent advances in computational power within HPC systems have enabled the simulation of macroscopic tissue arrangements. In line with this, we hereby present our work using Cells in Silico (CiS), a high performance framework for large-scale tissue modeling previously developed by us [1]. Based on both a cellular potts model and an agent-based layer, CiS is capable of accurately representing many physical and biological properties, such as individual cell shapes, cell division, cell motility etc. Working closely with experimental collaborators, we focused our studies on tumor spheroids, i.e. spherical aggregates composed of thousands of individual cells, which are one of the main workhorses of tumor cell analysis. Supplemented by experimental data on such spheroids, we parameterized our model, and, following this, were able to investigate the invasion dynamics and their dependence on the ECM density. We further aim to apply our model to data on spheroid fusions to investigate collective flow within the tissue.

[1] Berghoff, M., Rosenbauer, J., Hoffmann, F. et al. Cells in Silico – introducing a high-performance framework for large-scale tissue modeling. BMC Bioinformatics 21, 436 (2020)

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Poster #430 **on-site**

Hybrid Simulations of Collagen Breakages Reveal Mechanical and Oxidative Buffering

Presenting author: **Benedikt Rennekamp**

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Co-author/s: Frauke Gräter

Structural proteins such as collagen and many other force-bearing biological materials have important functions by carrying load and providing stability, but also in signaling. For example, we recently found that excessive mechanical load can lead to covalent bond scissions and the creation of mechanoradicals inside collagen fibrils. On the molecular scale, the implications of bond ruptures for the mechanical properties and subsequent biochemical reactions are yet to be determined. In such complex hierarchical structures, hybrid approaches spanning multiple scales are required to get a comprehensive understanding of the ongoing processes.

For this reason, we previously developed and presented here a hybrid Kinetic Monte Carlo / Molecular Dynamics (KIMMDY) simulation scheme featuring bond ruptures that allows to investigate the link between mechanical stress, breakages, and the subsequent dynamical response.

Furthermore, we now developed a statistical physics based model on the fibrillar scale, which enables us to understand and expand our results from the molecular scale to a mesoscopic fiber.

With KIMMDY, we investigated bond ruptures in a multi-million atom system of tensed collagen. Our simulations show a clear concentration of homolytic bond scissions near chemical crosslinks in collagen. Having a higher rupture propensity on one of the two crosslinks sites, a sequential rupturing mode there can act as a mechanical buffer mechanism by releasing additional length of the stressed strands. Integrating this hypothesis into the fibril-scale model, we conclude that this mechanism is a trade-off: Mechanically, between stability and elasticity of the fiber. Chemically, between less but unspecific ruptures, leading to damaging radicals everywhere in the fibril, and more but concentrated rupture sites, for which oxidative stress can be buffered more easily.

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Poster #436 **on-site**

A Continuous Complete RNA Translocation Cycle by the DEAH-Box Helicase Prp43 in Atomic Detail

Presenting author: **Robert A. Becker**

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Co-author/s: Jochen S. Hub

Understanding conformational cycles of complex macromolecular machines in atomic detail remains a central goal of molecular biophysics. Here, we focus on helicases that are crucial for every living organism to carry out functions such as DNA/RNA transcription, translation, DNA/RNA repair,recombination and splicing. The largest group among helicases is the Superfamily 2 (SF2), which includes the DEAD- and DEAH-box helicases as key players in the splicing pathway. Despite the wide interest in understanding the detailed mechanism of ssRNA translocation during splicing, the exact movements are still unknown. Using molecular dynamics simulations and enhanced sampling techniques, we observed a complete RNA translocation cycle of the DEAH-box helicase Prp43 in atomic detail. The simulations reveal the collective behaviour of the three main domains RecA1, RecA2and CTD, like the detachment and the formation of the interface of the RecA domains or the rotation of the CTD. Additionally, the simulations give detailed insight in the essential and atomistic processes during the large domain motions,e.g. a movement cascade induced by an arginine finger in the ATP binding side, the conformational change of a serine loop to a helical state, the cleavage and formation of various hydrogenbonds, including the so called Hook-loop and Hook-turn, the behaviour of the ssRNA during the process and more.

Poster #439 **on-site**

Predicting Ion Channel Conductance from Dissipation-Corrected Targeted MD and Langevin Equation Simulations

Presenting author: **Miriam Jäger**

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Co-author/s: Steffen Wolf

To gain insight into the molecular mechanisms of ion transfer through membrane ion channels we used dissipation-corrected targeted MD [1], which applies a moving distance constraint to enforce rare transitions, and yields both free energies and friction factors along the constraint coordinate. As test system, we investigated potassium diffusion through the gramicidin A channel. Performing a non-equilibrium principal component analysis on backbone dihedral angles we find coupled protein-ion dynamics occurring during ion transfer. The resulting free energy profiles correspond well to predictions from other biased simulation methods. Using these free energy and friction profiles along the channel as input for Langevin equation simulations [2] with an incorporated external electric field enables the prediction of macroscopic observables in the form of I–V characteristics.

[1] Wolf, S., Stock, G., J. Chem. Theory Comput. 14, 6175-6182 (2018)

[2] Wolf, S., et al. Nat. Commun. 11, 2918 (2020)

further information see Jäger, M., et al. , J. Chem. Theory Comput. 2022, 18, 1, 494–502 (2021)

Poster #440 **online**

Understanding Excited State Properties of Host Materials in OLED

Presenting author: **Samaneh Inanlou**

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Co-author/s: Rodrigo Cortés-Mejía, Ali Deniz Özdemir, Sebastian Höfener, Wim Klopper, Wolfgang Wenzel, Weiwei Xie, Marcus Elstner

In phosphorescent organic light-emitting diodes (PhOLEDs), amorphous materials such as 4,4-bis(carbazol-9-yl)-2,2-biphenyl (CBP) have been used as host materials for phosphorescent dopants. The host material in the emitting layer serves as a recombination center for holes and electrons to utilize emissions from the electronically excited states of molecules. In PhOLEDs, host materials are used to transfer excitation energy and generate the exciton in the emissive layer. Therefore, the fundamental understanding of the excited-state properties of host materials is the key for the design of high efficient PhOLEDs. The time-dependent scheme of LC-DFTB (TD-LC-DFTB) has been successfully parameterized and benchmarked for a test set of small organic molecules involving charge-transfer excitations. It is found that the TD-LC-DFTB gas-phase spectrum is in good agreement with the GW-BSE spectrum, indicating TD-LC-DFTB is an accurate method in calculating the excitation energies of CBP.

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Poster #442 **on-site**

Identifying The Metastable States

Presenting author: **Noosheen Rajabzadehtahmasebi**

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Co-author/s: Gerhard Stock

Markov state models are a popular tool to describe molecular processes. However, based on clustering methods (k-means and density-based clustering) classifying high-dimensional molecular dynamics data by usually hundreds of so-called microstates, they are too complex to grasp the essential information hidden in the data [1]. To this end, we apply coarse-graining methods, which aim to reduce the model from hundreds of microstates to a man-ageable set of only a few macrostates. Although these methods reduce the quantitative accuracy of the original model, they facilitate the investigation and allow us to study a more manageable state-space [1]. In this study, we investigate three different methods of coarse-graining of micro- into macrostates: Density-Based Clustering [2], Most probable Path [3], and Perron-Cluster Cluster Analysis [4]. These methods have been implemented thoroughly on our test systems: Alanine Dipeptide and Villin Headpiece(HP35). By this comparison, we seek to find an optimal coarse-graining method that gives us a well-defined state structure while retaining the correct timescales.

[1] L. M. Gregory R. Bowman and X. Huang, The Journal of Chemical Physics 139, 121905 (2013).

[2] F. Sittel and G. Stock, Journal of Chemical Theory and Computation 12, 2426 (2016), pMID: 27058020.

[3] A. Jain and G. Stock, Journal of Chemical Theory and Computation 8, 3810 (2012), pMID: 26593022.

[4] J.-H. Prinz, B. Keller, and F. Noé, Phys. Chem. Chem. Phys. 13, 16912 (2011).

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Poster #447 **on-site**

Free Energy Calculation of Peptide Binding to Lipid Droplets

Presenting author: **Mareike Oellers**

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Co-author/s: Chetan S. Poojari, Jochen S. Hub

Lipid droplets (LDs) are cell organelles found in all eukaryotes. Their surface is peppered with membrane proteins, through which they are involved in a variety of metabolic functions, primarily the storage and distribution of energy. Many of the constituent interactions have been observed experimentally; for example membrane trafficking, vesicle docking, endo- and exocytosis, inflammatory responses, and exploitation by pathogens.

However, many fundamental questions about LD biogenesis and function are still unanswered, such as: How are proteins targeted to LDs? What makes the LD monolayer surface distinct from the outer leaflet of a bilayer membrane, especially that of the endoplasmic reticulum (ER)? How do proteins sense these differences?

From previous experimental work (e.g. Chorlay and Thiam 2019, JCB https://doi.org/10.1083/jcb.201907099) we know protein affinity seems - perhaps surprisingly - dependent on both membrane and core properties, but the details of this interplay warrant further investigation. This work seeks to explore how binding specificity is achieved for mono- and bilayers of various compositions via coarse-grained simulations of a number of archetypal amphipathic helices (AHs) interacting with these LDs, using umbrella sampling to calculate a potential of mean force (PMF).

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Poster #448 **on-site**

Complementary or Competing Interactions? Effects of DPRs and RNA on FUS Condensates, and Their Implications in ALS Progression.

Presenting author: **Mark Driver**

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Co-author/s: Jasper Postema, Patrick Onck

Membraneless organelles (MLOs) within cells provide organisation of the intracellular environment through the process of liquid liquid phase separation (LLPS). The proteins that form these condensates often have low complexity domains (LCDs) which are intrinsically disordered. Interactions between LCDs, RNA and RNA binding domains drive assembly of these biomolecular condensates. The Fused in Sarcoma (FUS) protein is an RNA binding protein (RBP) that undergoes LLPS with RNA as part of normal activity in healthy cells. The high degree of disorder in the LCDs also makes them aggregation prone, forming solid-like deposits. The formation of solid like aggregates by FUS, has been linked to the diseases amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), which have no cures and ineffective treatments. Dipeptide repeat proteins (DPRs), caused by repeat expansion disorders of RNA. polyPR and polyGR DPRs have been shown to promote aggregation of disease linked proteins, like FUS.

We have previously developed coarse-grained molecular dynamics (CGMD) models that enable the simulation of large collections of biomolecules over sufficient timescales to study essential cellular processes. The aim of this work is to explore the change of FUS condensate properties upon inclusion of RNA or DPRs, identify the key interactions driving condensate formation and structure, and the implications for aggregation propensity. The results of simulations on FUS-RNA and FUS-DPR mixtures using our 1 bead per amino acid (1BPA) and newly developed 3 bead-per-nucleotide (3BPN) models will be presented.

Poster #452 **on-site**

Simulation of Liquid Jet Explosions and Shock Waves Induced by X-Ray Free-Electron Lasers

Presenting author: **Leonie Chatzimsagas**

Saarland University, Department of Theoretical Physics, Computational Biophysics Group, Saarbrücken, Germany

Co-author/s: Jochen S. Hub

X-ray free-electron lasers (XFELs) produce X-ray pulses with very high brilliance and short pulse duration. These properties enable structural investigations biomolecular nanocrystals, and they allow resolving the dynamics of biomolecules down to the femtosecond timescale. To deliver the samples rapidly into the XFEL beam, liquid jets are used. The impact of the X-ray pulse leads to vaporization and explosion of the liquid jet, while the expanding gas triggers the formation of shock wave trains traveling along the jet, which may affect biomolecular samples before they have been probed. Here, we used atomistic molecular dynamics simulations to reveal the structural dynamics of shock waves after an X-ray impact. Analysis of the density in the jet revealed shock waves that form close to the explosion center and travel along the jet. A trailing shock wave formed after the first shock wave, similar to the shock wave trains in experiments. Although using purely classical models in the simulations, the resulting explosion geometry and shock wave dynamics closely resemble experimental findings, and they highlight the importance of atomistic details for modeling shock wave attenuation.

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Poster #453 **online**

Unraveling Large-Scale Motions and Membrane Binding of Dynamin-Like Proteins by Molecular Simulations

Presenting author: **Jennifer Loschwitz**

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Co-author/s: Wibke Schumann, Birgit Strodel

After Toxoplasma gondii infection, some murine guanylate binding proteins (mGBPs), which belong to the superfamily of dynamin-like large GTPases, are highly upregulated. The mGBPs can form multimers and assemble on the membrane of the parasitophorous vacuole, which leads to membrane disintegration. For understanding the membrane-damaging mechanism, we perform a multitude of ordinary and enhanced molecular dynamics (MD) simulations. We focus our studies on the two proteins mGBP2 and mGBP7, because they are investigated in parallel using different experimental techniques by our CRC 1208 collaboration partners. Hamiltonian replica exchange MD simulations of mGBP2/7 revealed that the proteins undergo large-scale hinge motions of up to 70 Å. To further explore this motion we applied umbrella sampling simulations to map the complete close ↔ open mechanism of this hinge motion, for which the bacterial dynamin-like protein was used since both end states are structurally available for this protein. We determined the energetic barrier of the fully conformational change to be 40 kcal/mol, which is accessible by GTP hydrolysis. Next, we will test whether the results remain valid for mGBP2. To unravel the lipid membrane-binding of mGBP2/7, we switched to cthe oarse-grained level and modeled different, experimentally tested membrane compositions. The major observations are (i) that mGBP2 has a higher membrane affinity than mGBP7, and (ii) that the membrane composition influences the membrane binding. The next step will be to simulate the membrane binding of mGBP2 and mGBP7 dimers.

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Poster #457 **online**

Study of the binding site dynamics, druggability and cryptic pocket formation in different human coronaviruses' main protease (Mpro)

Presenting author: **Ahmed Adel Ezat**

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Coronaviruses are a diverse family of enveloped RNA viruses. There are seven human viral species (229E, OC43, NL63, HKU1, SARS - CoV, MERS and SARS – CoV2) identified till now. Human CoVs cause mild to severe respiratory system infections. Till now, there is no available broad spectrum antiviral and there are ongoing efforts to find a suitable one. 3CLpro or main protease (Mpro) is a suitable target for deigning viral inhibitors. With the aid of different computational methodologies, we aim to investigate binding site dynamics, energetics, druggability and cryptic sites formation of different human corornviruses to foster the design of a broad spectrum antiviral. Cryptosite server is used to infer the likelihood of cryptic site regions while FTMap protocol is used to identify druggable hotspot regions around these sites. The dynamics of binding sites are simulated with an enhanced sampling technique L-RIP (Langevin rotamerically induced perturbations) MD approach. For most of the viruses, some of the predicted cryptic pockets coincide with the binding regions of SARS – CoV and SARS – CoV2 nM binders identified till now, such as the anchor site (Glu166, Pro168, Gln182, Gln189 and Thr190) which can accommodate a large hydrophobic moiety and around the catalytic dyad (His41 and Cys145). There is no predicted region around Thr25 and Thr26 in SARS – CoV2 compared with SARS – CoV. These regions confer high affinity for hydrogen bonding and nonbonded interactions with probe molecules used in FTMap scanning. The dynamics of binding site shows different flexibility regions with different shape and size.

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Poster #459 **on-site**

Exploring Protein-Protein Interactions at High Concentrations using the Martini3 Coarse-Grained Force Field

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Co-author/s: Lars Schäfer

High-concentrations protein solutions are complex systems with slow dynamics. Investigating these systems in molecular dynamics (MD) simulations requires runtimes at a microsecond time scale or more to sufficiently sample many possible conformations. The computational resources necessary to perform these simulations in an all-atom approach are significant. The method of coarse-grained MD simulations vastly increases the time scale that is computable but introduces further serious approximations to describe the molecular system of interest.

Here, we investigated the performance of the Martini 3 coarse-grained force field in comparison with AMBER and CHARMM-based force fields. We explored the interaction of the Fab domains of the monoclonal antibodies trastuzumab and omalizumab in water and different cosolvent concentrations of Arg/Cl, Na/Glu, and Arg/Glu in aqueous solution in the different force-fields and evaluated the capability of Martini 3 to study protein-protein interactions.

Poster #466 **online**

Kinetics of Azochignolin Beta-Hairpin Folding

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AzoChignolin is a photoswitchable mutant of the mini-protein Chignolin, created by incorporating the azobenzene molecule AMPP into its loop region. When AMPP is in its trans-isomer, AzoChignolin remains denatured, yet in its cis-isomer it folds similar to Chignolin into a beta-hairpin. Utilizing explicit long-time scale molecular dynamics simulations of AzoChignolin and Chignolin in MeOH and water, we estimated Markov models to examine and compare the folding kinetics between cis-AzoChignolin and Chignolin. We show that while AzoChignolin manages to replicate Chignolin's beta-hairpin well, the folding kinetics of the two systems are quite different, with highly differing intermediate states, particularly Chignolin is able to fold in MeOH into an alpha-helical intermediate which is impossible to form in AzoChignolin due to its centrally located AMPP. Using the Markov models we show that AzoChignolin's kinetics are generally faster, specifically when comparing the two main microfolding processes of hydrophobic collapse and turn formation.

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Poster #469 **online**

Unfolding of the VemP-Helix Inside the Ribosomal Exit Tunnel: Metadynamics Approach

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Co-author/s: Michal H. Kolář

Ribosomes are responsible for proteosynthesis, during which the messenger ribonucleic acid is translated into a sequence of amino acids. The nascent chain leaves the ribosome through an exit tunnel located within the large ribosomal subunit. In the exit tunnel, cotranslational folding takes place which may regulate the translation by so-called stalling. Vibrio export monitoring polypeptide (VemP) is an example of such regulatory protein causing translational arrest by adopting compact structure inside the tunnel. Although VemP is well studied structurally, the energetics of cotranslational folding of its two α-helices remains elusive.

We focus on the C-terminal α-helix of VemP, which is directly involved in the stalling mechanism. Recent work of Dr. Kolář et al. suggested that the tunnel environment favors the helical structure and that the helix unfolding likely occurs on timescales longer than microseconds. To identify possible free-energy barriers of VemP unfolding, we carried out all-atom metadynamics simulations and investigated several collective variables. The simulations with a bias on the intramolecular hydrogen bonds showed only slow unfolding of the helix. On the other hand, when we biased the intermolecular interactions between the helix and tunnel walls, the helix unfolded smoothly and faster. Our results highlight the importance of the ribosome exit tunnel in determining folding/unfolding equilibria of nascent proteins.

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Poster #470 **online**

Liquid-Liquid Phase Separation in Gene Transcription

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Liquid-Liquid phase separation plays an important role in the formation of localized nuclear hubs of RNAP II during the transcription process. Recent experimental studies revealed that the Carboxy terminal domain (CTD), the largest subunit of RNAP II, is a low complexity domain, and has a very strong tendency to phase separate. Our research is focused on understanding the molecular basis of phase separation of CTD using multiscale molecular dynamics simulation methods. CTD is conserved in eukaryotes with the repeats of the heptapeptide sequence. However, there are small differences in CTD sequences of different species. We investigated how the CTD phase separation is affected by such differences in CTD sequences using coarse-grained molecular dynamics simulations. Our investigations indicate that deviation from the ideal heptapeptide sequence has less tendency to phase separate, which suggests that these deviations from the ideal heptapeptide repeats are important for responsive regulation of transcription. Also, the effects of temperature on CTD phase behavior and the influence of polymer length on critical temperature are as expected from Flory-Huggins theory. Moreover, we are looking at how phosphorylation of CTD and the presence of other biomolecules can influence CTD phase behavior and regulate gene transcription. Hyper-phosphorylation prevents phase separation as the negatively charged phosphate groups repel each other. However, CTD is hyperphosphorylated in transcription elongation. We show how hyperphosphorylated CTD might co-phase separate in elongation with HRD of Cylin T1 in accordance with the experiment. To explore more on this, we studied the phase behavior of CTD and phosphorylated CTD in the presence of HRD and the results show that they co phase separate into a large cluster, but do not mix, which may help to physically distinguish between the initiation and elongation stages of transcription. A precise understanding of the molecular basis of interactions that leads to phase separation could be possible by employing atomistic simulations and this will, in turn, lead to improved coarse-grained simulation models.

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Poster #472 **on-site**

Path Probability Ratios for Langevin Dynamics – Exact and Approximate

Presenting author: **Bettina Keller**

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Co-author/s: Stefanie Kieninger, Luca Donato

Enhanced sampling techniques generate trajectories at a biased potential, such that the exploration of the molecular state space and transitions across barriers is sped up. Path reweighing techniques recover the transition rates of the unbiased system from the biased trajectories by calculating the path probability ratio. Path reweighing requires that (a) the trajectory has been generated using an integration scheme for stochastic dynamics, and (b) that the formula for the path probability ratio has been tailored for that specific integration scheme. This makes them technically difficult, because a separate reweighing factor for each stochastic integration scheme is needed. Most published path probability ratios are derived for overdamped Langevin dynamics. Yet, overdamped Langevin dynamics is rarely used in MD simulations. Instead a variety of integration schemes for Langevin dynamics are used. Simply applying the path probability ratio for overdamped Langevin dynamics to a Langevin trajectory introduces a sizeable error.

Here we derive the path probability ratio for the integration scheme of Langevin dynamics implemented in OpenMM. We demonstrate that it to accurately reweights Langevin trajectories. By comparing this path probability ratio to path probability ratio for overdamped Langevin dynamics, we then derive an approximate and general path probability ratio for Langevin dynamics. This approximate path probability ratio depends on the random number sequence used to generate the Langevin trajectory and on the bias potential. Because it is independent of the integration scheme, it removes requirement (b) and can be used as multi-purpose probability ratio for any Langevin trajectory. We show that the approximate path probability ratio yields highly accurate results, and discuss the limits of the approximation.

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Poster #477 **on-site**

Scrutinizing the Hydration Shell of Proteins from SAXS and MD Simulations: Effects of Water Models and Force Fields

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Co-author/s: Jochen S. Hub

Proteins in solution are surrounded by a hydration shell consisting of several hydration layers, formed by the water molecules near the protein surface. Because the hydration shell influences the structure and activity of a protein, it may be considered as a functionally relevant part of the protein. However, the structure of the hydration shell remains poorly understood. Small-angle scattering (SAS) in solution using X-rays (SAXS) or neutrons (SANS) in principle provide information on the hydration shell, since both the radius of gyration (Rg) and the zero-angle scattering (I0) depend on the hydration shell contrast relative to the bulk solvent. Here, we used MD simulations and explicit-solvent SAXS/SANS calculations to investigate how variations of the hydration shell manifest in variations of Rg and I0. SAXS/SANS

curves were computed for several proteins (xylanase, lysozyme, GB3 domain, and RNaseA), protein force fields, and water models. Our calculations reveal that different proteins exhibit different hydration layer contrasts. In addition, the water model significantly influences the hydration layer. Specifically, recent water models with increases dispersion interactions impose increased Rg and I0 as compared to a standard TIP3P model. Together, our calculation provides a novel route for comparing hydration layers between simulation and experiments, for validating water models, and, thereby, for scrutinizing the hydration layer of proteins.

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Poster #478 **on-site**

Mechanoactivation of Abl Kinase Using Force-Probe Molecular Dynamics Simulations

Presenting author: **Svenja de Buhr**

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Co-author/s: Frauke Gräter

The non-receptor tyrosine kinase Abl is involved in cell proliferation, survival and development and has an increased activity in stretched cells. The latter is independent of the known upstream kinases Src, Fyn and Yes, raising the question whether Abl could act as a direct mechano-sensor. Abl has low basal activity because its two Src homology domains tightly bind to the kinase domain. Force can be transmitted to Abl from the cellular membrane through its N-terminal myristoyl modification and from the cytoskeleton through its C-terminal F-actin binding domain. We used Molecular Dynamics simulations to show that force acting on the N-terminus of the SH3 domain and the C-terminus of the kinase domain results in the release of both inhibitory Src homology domains from the catalytic kinase domain. The kinase domain remains largely intact with limited unfolding at its C-terminus, indicating that it can be activated by force.

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Poster #480 **on-site**

Investigation of Activation and Inhibition Mechanism in TREK-1 and TREK-2 Potassium Channels Using Molecular Dynamics Simulations

Presenting author: **Berke Türkaydin**

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Co-author/s: Han Sun

The molecular mechanism of the ion permeation process for two-pore-domain (K2P) channels, a family of potassium channels, is mainly controlled by the selectivity filter that acts as a primary gate. Previous studies on the K2P channels showed that ion occupancy in the selectivity filter is one of the essential factors for the activation mechanism. Recent crystal structures showed several aspects of the TREK channels, members of the K2P family such as ion-occupied selectivity filter, which enable us to deduce how the ion permeation event occurs. However, the activation and inhibition mechanism of TREK channels remains elusive. In this project, we aimed to investigate the activation and inhibition mechanism of TREK-1 and TREK- 2 potassium channels with the help of molecular dynamics (MD) simulations. We first evaluated the structural stability of different MD simulation setups. During the MD simulations, we investigated the impact of ligand binding on the conformation dynamics of the channel. Experimental studies revealed that attaching methanethiosulfonate (MTS) to the C-terminus influences the activation or inhibition of the channel relying on the chemical structure. We attached different MTS molecules to the C-terminal domain of the protein, and analyzed the structural changes of the channel, especially in the selectivity filter (SF) part by various MD analysis tools. Finally, we used the computational electrophysiology method to simulate the ion flux of the TREK-2 channel. Together, we showed in this project that the conductivity of the channel depends on the conformation state of the C-terminal and the C-terminal domain has a reciprocal relationship with SF of the protein, which is probably essential for the channel conductivity.

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Poster #481 **on-site**

The Influence of Dynamical Degrees of Freedom on Compass Sensitivity: A Comparison between Plant and Migratory Bird Cryptochrome

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Co-author/s: Siu Ying Wong, Luca Gerhards, Fabian Schuhmann, Daniel R. Kattnig, P. J. Hore, Ilia A. Solov'yov

The magnetic compass of migratory birds is thought to rely on the radical pair mechanism operating inside a cryptochrome blue-light photoreceptor [1]. It is imperative that the radical pair exists in a nonequilibrium coherent state, long enough for the Earth's magnetic field to have an influence on the underlying coherent spin dynamics. Several interactions weaken the coherence of the radical pair in a process called spin relaxation [2]. Here, we investigate several dihedral and librational angles in the flavin adenine dinucleotide (FAD) and tryptophan (Trp) radical pair inside cryptochrome from European robin in order to characterise spin relaxation dependent on thermal motion. Through analysis of cryptochrome dynamics, we have established the contribution of different degrees of freedom to the coherence lifetimes of potential radical pairs inside cryptochrome. This analysis relies on the time-dependent hyperfine interactions for the FAD and Trp radicals, which permitted calculating the quantum yield anisotropy of the radical pair reactions in a magnetic field. The quantum yield anisotropy, which is a measure for the sensitivity of the birds' magnetic compass, was compared for cryptochrome-based magnetoreceptors from European robin and thale cress to conclude if one is significantly better in perceiving the magnetic field than the other.

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Poster #489 **on-site**

Correlation-Based Feature Selection to Identify Functional Dynamics in Proteins

Presenting author: **Daniel Nagel**

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Co-author/s: Georg Diez, Gerhard Stock

The function of proteins is closely linked to their conformational changes. To model and interpret them, it is essential to identify suitable features, such as backbone dihedral angles or interresidual distances. However, in this high-dimensional feature space – in addition to the motion of interest – one finds uncorrelated motions described by small subsets of features, which poses a difficult challenge for the subsequent dimensionality reduction.

In the following we present an effective and scalable correlation-based feature selection method (MoSAIC) that identifies functional dynamics in the feature space and separates it from noise in order to facilitate the further analysis. To demonstrate the virtues and possible drawbacks, we adopt the well-established folding of villin headpiece (HP35) and the functional dynamics of T4 lysozyme.

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Poster #493 **on-site**

Binding of Oxygen at the Qo-Site of the Human bc1-Complex may Lead to Formation of Superoxide

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Co-author/s: Ilia A. Solov'yov

The dimeric bc1-complex embedded in the inner membrane of mitochondria is a relevant part of the respiratory chain in a mitochondrial cell of eukaryotes [1]. With different electron transfers via oxidation and reduction at the Qo- and Qi-site in this protein complex, it contributes to the metabolic system of the cell. Specifically, the protein complex pumps protons across the membrane to maintain an electrostatic potential, which is in turn used to drive ATP synthesis. This molecular machinery, however, is suspected to be a source of superoxide, which is toxic to the cell, even in minuscular quantities, and believed to be a factor in aging [1,2].

Through molecular dynamics simulations, we investigate here the migration of molecular oxygen in the human bc1 complex in order to identify possible reaction sites that could lead to superoxide formation. The investigation follows an earlier study of the bc1 complex from Rhodbacter capsulatus [3-5] and reveals several important differences. Specifically, we characterize the differences in the two monomers of the human bc1 complex and determine the oxygen diffusion pathways that could lead to the sites where O2 could be efficiently converted to superoxide, thereby disturbing the regular functioning of the bc1 complex.

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Poster #496 **on-site**

Specific and Non-Specific Protein-Protein Interactions for Beta-Lactoglobulin

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Co-author/s: Mariana Kozlowska, Wolfgang Wenzel

Beta lactoglobulin (BLG) is the major whey protein found in milk and as such it has wide importance in the food industry. BLG is a well-characterized and well-understood model system, proven to attain its monomer-dimer equilibrium strongly dependent upon the pH and ionic strength of the solution. BLG monomers are dominantly present at pH≤3 and at pH > 8, otherwise, dimers and higher oligomers are present.[1] Here, electrostatic interactions play the key role for protein-protein interactions, as many amino acids of BLG have pH-dependent charge states. Understanding the BLG dimerization process on all-atom scale is important both from scientific and technological perspectives, and in depth studies are needed to fully elucidate this process.

In this study, we use a novel combination of different techniques to estimate the extent of specific and non-specific of intermolecular interactions in BLG system.[2] From the theoretical point of view, we have performed umbrella sampling MD simulations with an all-atom force field to calculate the change of the free energy of dimerization of BLG monomers as a function of pH (pH 3 and pH 7) and NaCl salt concentration (10 mM and 100 mM). In addition, we have used our recently developed xDLVO-CG model[3] to calculate second osmotic coefficients (B22), which correlate with the solubility of proteins regulated by non-specific interactions. xDLVO model uses coarse grained protein structures and efficiently samples 1328 different starting protein configurations, therefore, permits to assess protein-protein interactions faster and for larger variety of solution conditions than it is possible with MD approaches. In the end, we show the subtle interplay between different specific and non-specific interactions of BLG and the relationship between them at technically relevant protein processing conditions.

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Poster #497 **online**

Finding Protein-Ligand Unbinding Pathways in dcTMD Simulations Using Distance-Based Clustering

Presenting author: **Victor Tänzel**

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Co-author/s: Steffen Wolf

The exploration of protein-ligand dynamics from fully atomic simulations is of immense interest, for example in drug design, yet remains unfeasible in unbiased molecular dynamics (MD). To trigger rare events, we employ dissipation-corrected targeted MD (dcTMD) simulations, in which a moving distance constraint biases a chosen reaction coordinate x. The method combines a Markovian Langevin equation with a second-order cumulant expansion of the Jarzynski equality. From the required constraint forces, a free energy profile $\Delta G(x)$ as well as a friction coefficient $\Gamma(x)$ are extracted.

Transitions often occur along multiple pathways. In order to find these pathways, we study distance-based clustering approaches combining a pairwise ligand RMSD with phylogenetic networks via the Neighbor-Net algorithm. Here we explore the capabilities of this approach with the example of the trypsin-benzamidine complex.

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Poster #498 **on-site**

C-Terminal Activation of USP48

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Co-author/s: Matthias Stein, Michael Naumann

Ubiquitin specific peptidase 48 (USP48) is a large, mostly nuclear isopeptidase with unique properties among the USP family. Its catalytic mode of action is to trim poly-ubiquitin chains to tetra-ubiquitin instead of a complete disassembly. Additionally, the activity is significantly diminished by the absence of its C-terminal domain. Structural details of USP48 are missing due to challenges in the crystallization, posed by conformational dynamics and large hydrophobic surface patches. However, the AlphaFold model as well as structural insights from the homolog enzyme USP7 suggest that the C-terminus might physically interact with the catalytic domain.

In this ongoing research project, we combine equilibrium molecular dynamics simulations of the catalytic domain with and without its C-terminus and in presence and absence of ubiquitin with kinetic studies on its activity also in response to small-molecule inhibitors. Additionally, a coarse-grained model of the full-length protein is developed and employed to estimate the dissociation free energy of the c-terminus using umbrella sampling. The results aim to shed light on the catalytic mechanism and to guide further crystallization efforts.

Poster #499 **on-site**

Permeability and Ammonia Selectivity Through Aquaporin AtTIP2;1 in Liquid and Gel Phase Lipid

Presenting author: **Deepak Kumar**

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Co-author/s: Tomas Kubar

Aquaporins are highly efficient transmembrane proteins that selectively, yet efficiently and passively allow water and other small solutes to pass through the lipid bilayer. Aquaporin AtTIP2;1 has been suggested to facilitate the permeation of water as well as ammonia across the vacuolar membrane of plants. Experimentally, it is suggested that the selective filter region play a pivotal role in the permeation of ammonia across the aquaporin. In this work, we are studying the permeabilities of water and ammonia across aquaporin AtTIP2;1in liquid phase lipid and gel phase lipid. We also want to compare the permeation of water in liquid phase lipid as well as gel phase lipid using enhanced sampling simulation. Similarly, we also want to study the penetration of ammonia in both phases. Our 1 µs molecular dynamics simulation shows that channels are open in both ways, in both phases of the lipid and the permeation of ammonia is in the direction of the flow of the water. At the same time, the permeation of ammonia is blocked or hardly any in the gel phase. Whereas permeation of ammonia in liquid phase lipid is substantial. We have also calculated the potentials of the mean force for the permeation of water along the pore of the aquaporins in both phases, revealing a low barrier to the permeation.

Poster #503 **online**

Computational Modelling of Transmembrane Pores from Mirror-Image Peptides

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The transmembrane pores based on α-helices remain relatively unexplored and emerging as a hot topic in nanobiotechnology and synthetic chemical biology.[1,2] Here, we show that unnatural amino acids can be incorporated by chemical synthesis into the peptides to build stable transmembrane pores. More specifically, we engineered alpha-helical pores, DpPorA and DcWza based on the bacterial pores PorACj and Wza.[3–5] The pore properties of DpPorA, specifically the single-channel conductance, are distinct from that of LpPorA. We suggest that stereo inversion of laevorotatory amino acids into dextrorotatory amino acids most likely alters the surface topology, helical packing and structural assembly of the pores leading to lower ion conductance of DpPorA. The similarity in the radii and electrostatic potentials for the DcWza and LcWza are in accordance with the similar conductance values of these two pores. The pores demonstrated here are a highly original system of outstanding general interest due to the unique protein architecture and potential applications in nanobiotechnology and nanopore chemistry, including DNA and peptide sequencing. Additionally, our findings may shed light on the mechanism of action of antimicrobial peptides.

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Poster #504 **online**

Peptide Elongation in Carbon Nanotube: An Atomistic Approach

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Proteins are the most ubiquitous biomolecules found in nature. In the first seconds of their existence, proteins are confined to the exit tunnel of the ribosome, the cell's protein assembler. One of the simplest confined spaces is the carbon nanotube (CNT). Under confinement, proteins behave differently than when free in solvent. For instance, the principles of protein translocation through the confined space are unknown. In this work, we have developed an automated pipeline to emulate the elongation and translocation of a peptide in CNTs. The pipeline is based on molecular dynamics simulations and computational alchemy and allows to elongate a peptide by one amino acid at a time. Two CNTs with diameters of 1.2 nm and 1.6 nm were investigated. We obtained multiple elongations of several uncharged 10-residue homopeptides (alanine, serine, glycine, threonine, phenylalanine, leucine, methionine) . In the narrower CNT, the polyserine translocated the slowest and formed a number of intramolecular interactions. On the other hand, polyglycine with fewer interactions elongated faster and reached the highest peptide length. In the wider CNT, peptides with larger side chains (leucine, phenylalanine, and methionine) were able to elongate further. Wider CNT also allowed more intramolecular interactions to be formed. Our results show that the translocation rates and final peptide lengths depend on both the CNT diameter and the polypeptide sequence. Future versions of the pipeline with charged peptides and biology-relevant environments may help us understand how proteins behave under confinement.

Poster #507 **online**

Conformational Transitions in the Catalytic Cycle of Cezanne-1

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Ubiquitinylation of the proteins, as one of the most commonly seen post-translational modifications, plays a pivotal role in many cellular processes. Conjugated ubiquitin moieties are selectively cleaved by deubiquitinylating enzymes (DUBs) according to the linkage between ubiquitin molecules. However, both activation and selectivity of DUBs have not yet been fully understood. The DUB Cezanne-1 selectively removes Lys11-linked polyubiquitin molecules. In DUB activation processes, different conformational states can be resolved experimentally but the mechanism of activation and the selectivity of recognition is only now being rationalized at the molecular level. Here, we study the substrate-assisted activation of Lys11-linked ubiquitin Cezanne-1 using full-atomistic microsecond-scale molecular dynamics simulations. MD simulations reveal transient intermediate states, which highlight the dynamic transitions of Cezanne-1 to prepare itself for the recognition and cleavage of specific polyubiquitin chains. Furthermore, it is also shown that ubiquitin-binding reduces the inter-residue distances within the catalytic triad that is in line with a substrate-assisted activation process. We also show that the zwitterionic charge state of Cezanne-1 is the physiologically-relevant one as both the structural fluctuations of the proximal ubiquitin and interatomic distances within the triad are further diminished.

To sum up, both the zwitterionic state of the catalytic triad and the binding of ubiquitin might facilitate the catalytic competency of Cezanne-1

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Poster #508 **on-site**

Study of the Slo1 Channel Gating Using Molecular Dynamics Simulations

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Co-author/s: Bert L. de Groot, Wojciech Kopec

Slo1 is a potassium channel that belongs to the type of 'big potassium', or BK channels. BK channels have an unusually high conductance rate for potassium ions, on the order of ~100 pS, and are activated synergistically by Ca2+ ions and voltage. For Slo1, CryoEM structures of its Ca2+-bound and Ca2+-free state are available. However, Slo1 in the Ca2+-free - supposedly closed - state lacks a constriction that would prevent the passage of potassium. Recent equilibrium MD simulations of Slo1 suggested that its pore undergoes a dewetting transition, thus inhibiting conductance (Jia et al., Nat. Commun 2018). In the present work, we elucidate the behavior of the Slo1 in the Ca2+-bound and Ca2+-free states in equilibrium and under applied voltage using MD simulations. Furthermore, by applying enhanced sampling techniques, we aim to observe the molecular details of the gating transitions between its functionally open and closed states.

Poster #510 **on-site**

Quantum Chemical Analysis of Ion Permeation in Potassium Channels

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Co-author/s: Bert L. de Groot

Potassium channels are the most widely distributed ion channels. It permeates potassium ions at a high rate. (150mA or an ion per ~10 ns). The MD simulated conductance is much lower than the experiment and the ion force field is typically blamed. We used force fitting and ab initio MD at the DFT level to specifically investigate the process of ion permeating the channel. The QM potential of mean force (PMF) pointed out that the MM force field overestimated the barrier in ion permeation which leads to a low permeation rate.

Poster #518 **on-site**

A QM/MM Molecular Dynamics Approach to the Light Harvesting Complexes

Presenting author: **Pooja Sarngadharan**

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Light-harvesting complexes (LHCs) collect energy from sunlight and transfer it to reaction centers with the help of intermediate antenna complexes. Lately, the quest for mechanisms of efficient excitation energy transfer (EET) in LHCs of plant systems is an attractive area of research. Excited state calculations of LHCs using the long-range corrected time-dependent Density Functional tight binding (LC-TD-DFTB) approach have recently shown to be rather accurate and efficient [1, 2]. Our study focuses on the EET in the antenna complexes of the photosystem II (PSII) where we employed a multiscale model. In this model, a quantum mechanical/molecular mechanical molecular dynamics (QM/MM MD) for the ground state dynamics of the systems. The excited state calculations were performed using LC-TD-DFTB in a QM/MM framework. From the excitation energy fluctuations, the spectral densities of the systems have been calculated and can be used as an input in density matrix propagation schemes to obtain spectroscopic properties and population dynamics. The spectral densities of the antenna complex CP29 show a good agreement especially in the high-frequency region with experimental spectral densities [3]. Furthermore, the absorption spectra of the LHC's have been calculated and compared to their experimental counterparts. These results based on QM/MM MD widen the scope for investigating EET mechanisms in large light-harvesting systems.

[1] B. M. Bold, et. al., Phys. Chem. Chem. Phys.22, 10500–10518 (2020).

[2] S. Maity, et. al., J. Phys. Chem. Lett.11, 8660–8667 (2020).

[3] S. Maity, P. Sarngadharan et. al., J. Chem. Phys.155, 055 103 (2021).

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Poster #519 **on-site**

High-Throughput Polymer Design with Martini 3

Presenting author: **Fabian Grünewald**

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Co-author/s: Fabian Grünewald, Paulo C. T. Souza, Siewert J. Marrink

Rational design of polymeric nano-materials powered by combinatorial polymer chemistry opens a new avenue to engineer custom fit-for-purpose materials especially promising for biomedical applications. However, navigating the structure-function landscape of polymers to find a composition that yields the desired properties is challenging due to the large variety of monomers available.[1] Combining experimental high-throughput (HT) protocols with machine-learning has been successful in overcoming this challenge.[2] On the other hand, HT screening of polymers by MD is expected to complement these approaches because it is typically less costly than synthetic exploration and gives access to properties not easily accessible by experiments. To facilitate such approaches we recently presented the polyply software suite[3]. Polyply provides a multi-scale graph matching algorithm designed to quickly generate simulation parameters for arbitrarily complex polymeric topologies and a generic multi-scale random walk protocol capable of setting up complex systems efficiently and independent of the target force-field or model resolution. Here we present our progress in utilizing polyply in combination with the coarse-grained Martini model (version 3) to realize HT screenings of polymers to explore their structure-function landscape.

[1] Gormley, A.J., Webb, M.A. Machine learning in combinatorial polymer chemistry. Nat Rev Mater 2021

[2] Tamasi, Matthew, Roshan Patel, Carlos Borca et al. Machine Learning on a Robotic Platform for the Design of Polymer-Protein Hybrids. Chemrxiv 2022

[3] Grünewald, F., Alessandri, R., Kroon, P.C. et al. Polyply; a python suite for facilitating simulations of macromolecules and nanomaterials. Nat Commun 2022

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Poster #523 **on-site**

Coarse-Grained Models for Intrinsically Disordered Domains, IDD, Ported into GROMACS: How Phosphorylation Shifts IDD Conformational Ensembles

Presenting author: **Camilo Aponte-Santamaría**

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Determination of the dynamics of intrinsically disordered proteins (IDPs) is essential to understand their function. Although all-atom molecular dynamics (MD) simulations have enabled a quantitative monitoring of the dynamics of these types of proteins at an unprecedented and valuable level of detail, they are still limited to relatively small and individual IDPs. Several coarse-grained models have been recently proposed to efficiently and accurately simulate complete single IDP chains and IDP condensates. These models involve non-bonded interactions which are different than the conventionally used-ones in standard biomolecular MD simulations. Implementations of these models exist in MD packages such as LAMMPS or HOOMD. Here, we report the port of three recent models HPS, CALVADOS, and MPIPI into the widely used MD software GROMACS. The port is applied to study the dynamics of the intrinsically disordered region of the inner centromere protein (INCENP), a part of the chromosome passenger complex playing a key role during mitosis. The disordered fragment of INCENP is about 440 aminoacids long and our coarse-grained simulations allowed us to systematically study the effect of the phosphorylation on this disordered region, backed up by all-atom simulations of individual short INCENP fragments (Martin, Aponte-Santamaría, et al. J Mol Biol. 434: 167387, 2022). Overall, we expect this port to complement other existing implementations of IDP coarse-grained models and to facilitate their use into a unifying MD framework within the GROMACS package.

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Poster #524 **online**

A Novel Approach for Targeting Specific State of a Protein that Emerges Under Disease Conditions: A Case Study on Phosphorylated Farnesyltransferase

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Co-author/s: Mustafa Guzel, Ozge Sensoy

Protein phosphorylation is one of crucial cellular regulatory mechanisms since activation/deactivation of many enzymes and receptors is regulated by this reversible post-translational modification. As a notable example, the phosphorylation of the α-subunit of heterodimeric farnesyltransferase (FTase) enzyme has been shown to increase in hyperinsulinemia which is related to cancer and diabetes [1,2]. As such, it impacts the structural and dynamical properties of phosphorylated proteins; however, the molecular mechanism has remained elusive. To address this, we performed a total of 18-microseconds molecular dynamics simulations on four different complexes of (non)-phosphorylated FTase, each of which is representative of the steps involved in the farnesylation process. We named these enzymatic steps as follows: apo (FTase), binary (FTase+FPP), ternary (Ftase+FPP+CaaX peptide) and, product (FTase+farnesylated CaaX peptide). As a result of the comparative study, we observed that phosphorylation strengthens the interaction between two subunits and triggers structural rearrangements in FTase. These are i) proper orientation of the FPP (farnesyl pyrophosphate) and the CaaX peptide, and ii) regulation of the catalytic zinc ion coordination in the active site, thus expediting the activity in binary and ternary. On the other hand, the opposite conformational rearrangements are observed in the product which might ease the release of the farnesylated peptide. We also identify a possible cryptic region on the phosphorylated FTase with reasonable binding pocket score. The consistency of our results with structural and biochemical data as well as emergence of a possible cryptic site on the phosphorylated FTase is promising and suggests that understanding the mechanistic impact of phosphorylation can help targeting of a specific state of the enzyme that emerges under certain disease conditions.

[1] Solomon et al. Biochemical and biophysical research communications 2001, 285, 161–166.

[2] Draznin et al. Endocrinology 2000, 141, 1310–1316.

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Poster #525 **on-site**

Constructing Large Scale Simulations using the Martini Force Field

Presenting author: **Jan Stevens**

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Co-author/s: Siewert-Jan Marrink

Molecular dynamics (MD) is a well established simulation method, which has successfully been applied to study a wide range of biomolecular processes. As a result of continuous improvements in both computational infrastructure and modelling methods we currently observe that the study of mesoscopic, multi-component systems become attainable. Here we present the use of our newly developed Martini 3.0 coarse-grained force field, to explore new spatio-temporal resolution using MD simulations. To construct these models special tools are required. Here, we present the preliminary outline for two of the tools we are currently developing.

Our first tool aims to construct a realistic Martini model for a prototypical cytoplasm, based on the minimal cell JCVI-syn3 created by the Venter lab. This tool constructs a quasi-equilibrated model consisting of thousands of proteins under crowded conditions.

Secondly, we present our genome builder project. This tool is based on Polyply, a versatile python suite facilitating the generation of input files for systems containing various macromolecules. The genome builder aims to facilitate the construction of complex polynucleotide structures in various all-atom and coarse-grained descriptions. Possible applications range from the modelling of entire virus capsids to simulating DNA-Protein complexes.

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Poster #528 **online**

Correlated Quantum MD for the Price of Semiempirical: Parameterisation of DFTB3 and Long QM/MM Simulations

Presenting author: **Mayukh Kansari**

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Co-author/s: Denis Maag, Fathia Idiris, Alexander Schug, Tomas Kubar, Marcus Elstner

Density functional tight binding (DFTB) is a semi-empirical quantum method, well known for its fast and accurate calculations. Because of its fast calculation it gives us the scope to run QM/MM simulations up to nanosecond timescales, which opens the door for us to explore wide variety of bio-chemical reactions which used to be difficult due to time-scale problem in expensive QM calculations. DFTB needs suitable parameters to run as in other semi-empirical methods. In case of DFTB we use two atom cantered parameters. Our latest "3OB" parameters for DFTB3 are capable enough to produce results same as B3LYP level. However reactions in biochemistry often surprise us with its uniqueness making fail our existing parameter. We came across two such problems - a) disulfide-thiol shuffling in immunoglobulin b) autophosphorylation of histidine. These two cases forced us to re-fit our existing 3OB parameters to fit best for capturing the reaction mechanism. So we parameterised some "special reaction parameter(SRP)" for these two cases and applied the same in protein in QMMM. We show applications in drug hydrolysis and kinase activity.

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Poster #529 **on-site**

Lipid Binding Specificity of Viral Fusion Proteins

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Co-author/s: Tobias Bommer, Jochen S Hub

Viral fusion proteins drive the fusion of viral and host cell membranes in a series of complex structural transition events. Although the structure of several fusion proteins has been solved, the characterization of viral protein-membrane interactions at atomistic resolution is still missing. Membrane interactions of fusion proteins are conserved and occur via fusion peptides (FPs) in class I and fusion loops (FLs) in class II/III proteins. Previously, we had characterized the glycerophospholipid binding in class II fusion protein glycoprotein C (gC) of Rift Valley fever virus (RVFV) [2] and the studies revealed a specific binding pocket for PC lipid. Here we aim to understand if a specific lipid-binding site also exists in class I and III viral fusion proteins and dependence of lipid headgroup type, tail length and degree of lipid tail unsaturation for protein binding. Molecular dynamics (MD) simulations is an excellent technique to understand how proteins associates with lipid membrane at atomistic resolution and here we make use of MD simulations to gain structural insights into lipid contact sites and membrane insertion of FP / FL residues.

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Poster #530 **online**

Dynamics of Actin-Binding Proteins on the Membranes

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The actin cytoskeleton generates a driving force to deform membranes during many cellular processes. One of the phosphoinositides, phosphatidylinositol 4,5-bisphosphate [PI(4,5)P2], regulates the activities of many actin-binding proteins (ABPs); however, the underlying molecular mechanisms have remained elusive. Here, we applied biochemical assays and atomistic molecular dynamics simulations to uncover the molecular principles by which ABPs interact with PI(4,5)P2-containing membranes. We reveal that ABPs demonstrate large differences in the affinities and dynamics of membrane interactions, and in the ranges of PI(4,5)P2 densities that they sense. Together, these findings suggest that the molecular mechanisms underlying ABP-membrane interactions evolved precisely to perform their specific functions in cytoskeletal dynamics.

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Poster #532 **online**

From Atomic Resolution Ensembles of Disordered Proteins to Simulations of the Condensates and Phase Behaviour of Neurodegeneration-Linked Proteins

Presenting author: **Lukas Stelzl**

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Co-author/s: Lisa M. Pietrek, Andrea Holla, Benjamin Schuler, Dorothee Dormann, Markus Zweckstetter, Gerhard Hummer

Liquid-liquid phase separation of disordered proteins and the resulting biomolecular condensates are key regulators of cells. A detailed understanding of the structure and dynamics of disordered proteins in dilute and condensed states will help elucidating their roles in health and disease. However, the inherent flexibility of disordered proteins and their condensates makes structural studies and their interpretation challenging. Atomistic molecular dynamics simulations could help to address this challenge, but the need for long simulations has stymied progress. To overcome this challenge, we adopt a hierarchical approach, building on ideas from polymer science, combining a highly accurate description of local structures with efficient sampling of possible global structures and importantly retain atomic resolution at each step. Our atomic-resolution ensembles of the disordered proteins α-synuclein and tau agree well with small-angle X-ray scattering and NMR data. For tau we find that, pathogenic P301 mutations shift the ensemble towards locally more extended structures, which may be more aggregation prone. Our modeling also suggests that the aggregation-prone hexapeptide motifs sample extended structures as in fibrils. We show how to rigorously incorporate experimental information when generating models of disordered biomolecules using importance sampling. With the same hierarchical framework, we can generate atomic-resolution models of condensates of disordered proteins for large-scale simulations. Our atomistic molecular dynamics simulations of condensates and coarse-grained simulation of the phase phase-behaviour of the neurodegeneration-linked protein TDP-43 suggests a molecular basis of how phosphomimicking mutations and phosphorylation shape TDP-43 condensates in health and disease.

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Poster #533 **online**

Accelerating the Detection of Allosteric Sites in FBDD

Presenting author: **Maria Nuria Peralta Moreno**

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Co-author/s: Jaime Rubio Martinez (IQTCUB), José Manuel Granadino Roldán (UJAEN)

Despite the demonstrated efficiency of available computational methods in the field of fragment-based drug discovery (FBDD), some drawbacks such as protein denaturation, ligand aggregation or allosteric binding sites detection, have not yet been completely solved.

Within this framework, a systematic semi-automatic new computational method has been developed to overcome the existing difficulties and accelerate the identification of allosteric sites without any previous knowledge of the experimental binding site. The method, based in fragment dissolved Molecular Dynamics (fdMD) applied to Gaussian Accelerated Molecular Dynamic simulations, has been conceived as a fast and efficient alternative to accelerate the detection of allosteric sites in FBDD, detecting and discarding spurious results.[1]

To test the effectiveness of the method, different targets such as Mcl-1 or urokinase have been employed, obtaining promising results.

[1] Cristian Privat; et al. Fragment Dissolved Molecular Dynamics: A systematic and efficient method to locate binding sites. Phys. Chem. Chem. Phys., 2021,23, 3123-3134. https://doi.org/10.1039/D0CP05471B.

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Poster #535 **on-site**

The Minimal Markov Model for Rotary Catalysis of F1-ATPase

Presenting author: **Yixin Chen**

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Co-author/s: Helmut Grubmüller

Understanding the mechanism of F1Fo-ATP synthase (F-ATP synthase) is essential for understanding the conversion and utilization of energy in life. Studies on isolated F1-ATPase (the soluble sector of F-ATP synthase) have established the rotary catalysis paradigm, or binding-change mechanism, which explains the ATP-hydrolysis mechanism of F1-ATPase. Although the fundamental idea of binding-change mechanism has been widely accepted, a unified, detailed picture for F1-ATPase function has not been achieved yet.

We constructed a group of models for F1-ATPase, within a framework of Markovian description that incorporates as few essential degrees of freedom as possible, to explore what is the minimal, consistent and thermodynamically complete Markov model that can explain four essential aspects of F1-ATPase function, namely, [ATP]-dependent turnover, near 100% chemo-mechanical coupling efficiency, nucleotide titration curves and dwell kinetics. Using experimental observations on the former three aspects as training data, we formulated a generally applicable parameter optimization approach based on Bayesian inference. Observations on dwell kinetics are used to cross-validate the models after parameter optimization.

We concluded that the minimal model within our Markovian framework requires 4 single-β conformations and inter-subunit interactions of the γ-subunit with two β-subunits to reproduce all essential aspects of F1-ATPase function under investigation. This model provides a quantitative understanding of the thermodynamics and kinetics of F1-ATPase function, reconciling the bi-site vs. tri-site controversy and assigning crystal structures to defined stages of the catalytic cycle.

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Poster #537 **on-site**

Fast Multipole Method for a Constant ph Algorithm in GROMACS

Presenting author: **Bartosz Kohnke**

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Co-author/s: Eliane Briand, Carsten Kutzner, Helmut Grubmüller

Molecular dynamics (MD) simulations of biomolecules with dynamic protonation changes have lately become increasingly important. Constant pH molecular dynamics (CPHMD) allows to dynamically alter the protonation during simulations to correctly model protonation probabilities at a fixed pH level. Typically CPHMD utilizes a λ-dynamics method with Hamiltonian scaling, where a fictitious λ-particle continuously interpolates between protonated and deprotonated Hamiltonian. The dynamics of the λ-particle depends on the local electrostatic environment of a protonatable site; however, the long-range nature of coulombic forces requires reevaluation of the complete Hamiltonian at each protonation state. This step becomes a prohibitive factor for efficient usage of CPHMD systems with many sites since pairwise interactions evaluation is the most performance-limiting factor in MD simulations. To obtain atomistic trajectories of proteins on biologically relevant timescales, MD utilizes efficient approximation algorithms. The most prominent one in the field is particle mesh Ewald (PME), which is extremely fast but lacks the flexibility to perform Hamiltonian recalculations efficiently. A slightly different approach to CPHMD is a charge scaling method, which allows a more efficient interpolation scheme and a proper PME utilization. However, to enable efficient λ-dynamics with Hamiltonian scaling, we implemented a fast multipole method (FMM). In contrast to PME, FMM utilizes a flexible tree structure that preserves local charge differences, and therefore it allows for very fast Hamiltonian recalculations. Here, we present our NVIDIA CUDA FMM for CPHMD. The FMM GPU implementation has been tailored for MD calculations. Its performance is about a third of that of highly optimized PME on a single GPU node. However, the FMM allows simulation systems with many protonatable sites with negligible computational overhead. Additionally, on larger exascale GPU clusters, where PME scaling breaks down, the efficiency of FMM for CPHMD should become even more apparent.

Poster #538 **on-site**

Capturing Aggregation Pathways of Cellulose I Microfibrils in Water by All-Atom Molecular Dynamics Simulation

Presenting author: **Thu Thi Minh Tran**

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Co-author/s: Adolfo B. Poma

The aggregation of native cellulose microfibrils, which is formed by 36-glucan chains, is a fundamental process in higher plants and also for industries. The characteristic stiffness, hydrophobicity and water-induced swelling of a fiber which is defined by a bundle of microfibrils, provides us with a strong natural and man-made material. The remarkable mechanical strength of cellulose reflects the arrangement of multiple β-1,4-linked glucan chains in a para-crystalline state.

In this work, we performed a series of atomistic molecular dynamic simulations to study the interrelations between the underlying microfibril bundle structure of cellulose Iβ under the influence of water. Moreover, to understand the aggregation process, we have performed a series of simulations of the microfibril in a complex with free cellulose chains. Gromacs package version 2020.4 was used for all computational works with Charmm36m force field and TIP3P water model. Non-bond interactions as hydrogen bonds, Van der Waals forces between cellobiose units in the fibrils and glucose in free chains were analyzed to understand the physical mechanism under the structure of a protofibril.

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Poster #624/#322 **online**

Diffusion of Cocaine through a Model Membrane: A Computational Approach

Presenting author: **Sangwar Wadtey Oung**

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Co-author/s: Nora Kremer, Safa ben Amara, Ali Zaidi, Thorsten Koslowski

We study the diffusion of cocaine through a DMPC lipid bilayer as an example of a protonable, amphiphilic molecule passing a biological membrane. Using classical molecular dynamics simulations, the free energy surfaces are computed applying the umbrella sampling technique for the protonated and the neutral molecule.

For the combined surface, we numerically solve the diffusion equation at constant flow and for time-dependent concentrations. We find a potential of mean force dominated by a barrier of 3.5 kcal/mol within the membrane, and a pH-dependent entry and exit barrier of 2.0 kcal/mol and 4.1 kcal/mol, respectively. This behaviour can be rationalized chemically by the amphiphilic nature of the molecule and the change of its protonation state while passing the membrane.

Diffusion through the barriers is 3.5 times slower than along the membrane, and the typical time scale of passage amounts to 0.1 ms. We discuss biochemical and medical implications of our findings, such as the mechanism of the drug passing the blood-brain barrier.

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Poster #671 **online**

finDr: A Web Server for in Silico D-Peptide Ligand Identification

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In the rapidly expanding field of peptide therapeutics, the short in vivo half-life of peptides represents a considerable limitation for drug action. D-peptides, consisting entirely of the dextrorotatory enantiomers of naturally occurring levorotatory amino acids (AAs), do not suffer from these shortcomings as they are intrinsically resistant to proteolytic degradation, resulting in a favourable pharmacokinetic profile. To experimentally identify D-peptide binders to interesting therapeutic targets, so-called mirror-image phage display is typically performed, whereby the target is synthesized in D-form and L-peptide binders are screened as in conventional phage display. This technique is extremely powerful, but it requires the synthesis of the target in D-form, which is challenging for large proteins. Here we present finDr, a novel web server for the computational identification and optimization of D-peptide ligands to any protein structure (https://findr.biologie.uni-freiburg.de/). finDr performs molecular docking to virtually screen a library of helical 12-mer peptides extracted from the RCSB Protein Data Bank (PDB) for their ability to bind to the target. In a separate, heuristic approach to search the chemical space of 12-mer peptides, finDr executes a customizable evolutionary algorithm (EA) for the de novo identification or optimization of D-peptide ligands. As a proof of principle, we demonstrate the validity of our approach to predict optimal binders to the pharmacologically relevant target phenol soluble modulin alpha 3 (PSMα3), a toxin of methicillin-resistant Staphylococcus aureus (MRSA). We validate the predictions using in vitro binding assays, supporting the success of this approach. Compared to conventional methods, finDr provides a low cost and easy-to-use alternative for the identification of D-peptide ligands against protein targets of choice without size limitation. We believe finDr will facilitate D-peptide discovery with implications in biotechnology and biomedicine.

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Poster #686 **online**

Molecular Mechanism of Inhibiting WNK Binding to OSR1 by Targeting the Allosteric Pocket of the OSR1-CCT Domain with Potential Antihypertensive Inhibitors: An In Silico Study

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Co-author/s: Parimal Kar

The oxidative-stress-responsive kinase 1 (OSR1) and the STE20/SPS1-related proline–alanine-rich kinase (SPAK) are physiological substrates of the with-no-lysine (WNK) kinase. They are the master regulators of cation Cl– cotransporters that could be targeted for discovering novel antihypertensive agents. Both kinases have a conserved carboxy-terminal (CCT) domain that recognizes a unique peptide motif (Arg-Phe-Xaa-Val) present in their upstream kinases and downstream substrates. Here, we have combined molecular docking with molecular dynamics simulations and free-energy calculations to identify potential inhibitors that can bind to the allosteric pocket of the OSR1-CCT domain and impede its interaction with the WNK peptide. Our study revealed that STOCK1S-14279 and Closantel bound strongly to the allosteric pocket of OSR1 and displaced the WNK peptide from the primary pocket of OSR1. We showed that primarily Arg1004 and Gln1006 of the WNK4-peptide motif were involved in strong H-bond interactions with Glu453 and Arg451 of OSR1. Besides, our study revealed that atoms of Arg1004 were solvent-exposed in cases of STOCK1S-14279 and Closantel, implying that the WNK4 peptide was moved out of the pocket. Overall, the predicted potential inhibitors altogether abolish the OSR1–WNK4-peptide interaction, suggesting their potency as a prospective allosteric inhibitor against OSR1.

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Poster #687 **online**

Comparative Structural Dynamics of Isoforms of Helicobacter Pylori Adhesin BabA Bound to Lewis b Hexasaccharide via Multiple Replica Molecular Dynamics Simulations

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BabA of Helicobacter pylori is the ABO blood group antigen-binding adhesin. Despite the considerable diversity in the sequence of BabA, it shows an extraordinary adaptation in attachment to mucosal layers. Multiple replica molecular dynamics (MD) simulations were conducted in neutral and acidic aqueous solutions to elucidate the underlying molecular mechanism of the BabA-glycan complexation. The conformational dynamics of Lewis b (Leb) in the free and protein-bound states were also investigated. The carbohydrate-binding site across the four isoforms was examined, and the conformational variability of the several vital loops was observed. The cysteine-cysteine loops and the two diversity loops (DL1 and DL2) were identified to play an essential role in recognizing the glycan molecule. The accommodation of the glycan in the binding site was also observed by an arrangement of several changes in secondary structure over the simulation length, specifically for the 17875 strain. However, in terms of binding affinity, the Spanish specialist strain (S831) shows a strong affinity by increasing the electrostatic contribution. Our study also reveals that the α1-2-linked fucose contributes most in the binding by forming several hydrogen bonds with multiple key amino acids. Overall, our study provides a detailed understanding of the molecular mechanism of Leb recognition by four isoforms of H. pylori that may help the development of therapeutics targeted at inhibiting H. pylori adherence to the gastric mucosa.

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Poster #688 **online**

Phosphorylation-Induced Conformational Dynamics and Inhibition of Janus Kinase 1 by Suppressors of Cytokine Signaling 1

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Co-author/s: Parimal Kar

The dysfunction of the JAK/STAT (Janus kinase/signal transducers and activators of transcription) pathway consequences several pathophysiological conditions, including autoimmune disorders. The negative feedback regulators of the JAK/STAT signaling pathway, suppressors of cytokine signaling (SOCS), act as a natural inhibitor of JAK and inhibit the aberrant activity. SOCS1 is the most potent member of the SOCS family, whose KIR (kinase inhibitory region) targets the substrate-binding groove of JAK with high affinity and blocks the phosphorylation of JAK kinases. Overall, we performed an aggregate of 13 μs MD simulations on the activation loop's three different phosphorylation (double and singles) states. Results from our simulations show that the single Tyr1034 phosphorylation could stabilize the JAK1/SOCS1 complex as well as the flexible activation segment. The phosphate-binding loop (P-loop) shows conformational variability at dual and single phosphorylated states. The principal component analysis and protein structure network analysis reveal that the different phosphorylation states and SOCS1 binding induce intermediated inactive conformations of JAK1, which could be a better target for future JAK1 selective drug design. The structural protein network analysis suggests that the com-pY1034 system is stabilized due to higher values of network hubs than the other two complex systems. Moreover, the binding free energy calculations suggested that pTyr1034 states show a higher affinity toward SOCS1 than the dual and pTyr1035 states. We believe that the mechanistic understanding of JAK1/SOCS1 complexation will aid future studies related to peptide inhibitors based on SOCS1.

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Poster #708 **online**

Investigation of the Second Harmonic Generation Responses of Di-8-ANEPPS in a Collection of Lipid Bilayers: A Combined Molecular Dynamics-Quantum Chemistry Study

Presenting author: **Charlotte Bouquiaux**

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The cell membranes perform diverse and essential functions that are controlled by the enormous lipid structure diversity. Among the different lipid classes, cholesterol has a strong influence on maintaining the correct fluidity and rigidity of the animals cell membranes, and so their functions. Therefore, having a tool to distinguish between membranes of various cholesterol content is helpful in the deeper understanding of lipid bilayers. In this work, we investigate three glycerophospholipid phosphatidylcholine (PC) lipids, namely dipalmitoylphosphatidylcholine (DPPC), 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC), and dioleoylphosphatidylcholine (DOPC) with different levels of cholesterol by analysing the second-harmonic generation (SHG) nonlinear optical (NLO) response of a probe molecule, di-8-ANEPPS inserted into the membranes. This technique as the advantage to be specific to interfacial region, like lipid bilayer, and used in conjunction with an ANEPP-like molecule, allows us rapid acquisition at relatively low laser power. Six independent 400ns Molecular Dynamics simulations were performed on both DPPC and DOPC lipids by varying the cholesterol mole fraction (from 0 to 0.66), and one on the pure POPC system, giving thirteen systems total. The effect of the cholesterol on the properties of the bilayer are studied, namely the thickness, the area per lipid, the hydrocarbon parameter and also the orientation of the diverse molecules within the membranes. All the analysis of the structural parameters of the bilayers studied converge toward one conclusion: as the mole fraction of cholesterol increases, the systems are more and more rigid. This is known as the condensing effect of cholesterol. The structural analyses are then confronted to the molecular NLO response, β, computed at the TDDFT/M06-2X/6-311+G* level, and in particular the contribution to beta parallel to the bilayer normal, β_ZZZ. Using the same methodology, the effect of the presence of (un)saturations(s) was also studied and highlighted the increase of β_ZZZ going from saturated to unsaturated lipids. This computational approach provides insights onto the link between the cholesterol content/presence of (un)saturation(s) and the diagonal component β_ZZZ of the first hyperpolarizability and so a first approach towards the unravelling of the changes due to the cholesterol content/presence of (un)saturation(s) of lipid bilayers.

Poster #715 **online**

Boron Nitride Nanosheets Can Induce Water Channels Across Lipid Bilayers Leading to Lysosomal Permeabilization

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While the interaction between two-dimensional (2D) materials and cell membranes is of key importance to the development of nanomedicines and safe applications of nanotechnology, still very little is known about the biological interactions of many emerging 2D materials. Here we investigate how hexagonal boron nitride (hBN) interacts with the cell membrane by combining molecular dynamics (MD), liquid phase exfoliation and in vitro imaging methods. MD simulations reveal that a sharp hBN wedge could penetrate a lipid bilayer and simultaneously form a cross-membrane water channel along its exposed polar edges, while a round hBN sheet does not exhibit this behavior. We hypothesize that such water channels could facilitate cross-membrane transport, with important consequences including lysosomal membrane permeabilization (LMP), an emerging mechanism of cellular toxicity that involves the release of cathepsin B and generation of radical oxygen species leading to cell apoptosis. To test this hypothesis, we prepared two types of hBN nanosheets, the former with a rhomboidal, cornered morphology and the latter with a round morphology, and exposed human lung epithelial cells to both hBN nanosheets. The cornered hBN with exposed polar edges resulted in a dose dependent cytotoxic effect, whereas round hBN did not cause significant toxicity, thus confirming our hypothesis. The described water channel mechanism suggests various applications including the development of hBN-based drug delivery systems and safe design of future advanced hBN containing composites and devices.

Poster #746 **online**

A QM/MM Computational Study on the Catalytic Mechanism of Ideonella Sakaiensis PETase

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Plastic accumulation is one of the main environmental issues of our time. Over the years, several enzymes with the ability to hydrolize plastic have been discovered and characterized.1 In 2016, two enzymes capable of degrading PolyEthylene Terepthtalate (PET) were discovered: IsPETase and IsMHETase, from Ideonella sakaiensis.2

In this work, the catalytic mechanism of IsPETase was studied by a subtractive ONIOM QM/MM methodology.3 The system was divided in two regions: the high-level (HL) layer, calculated with density functional theory (DFT), and the low-level (LL) layer, calculated with molecular mechanics (MM). The HL layer included the catalytic residues (Ser160, Asp206, His237), the oxyanion hole, and three stabilizing residues we have found to highly impact the mechanism.

The reaction was found to progress in four distinct steps, divided in 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, and the full energy profile of the catalytic reaction was mapped out. The determined turnover rate agrees with the current experimental findings regarding kinetics. Furthermore, in this study, we have highlighted the importance of using a large QM region and clarified the role of three residues interacting with catalytic aspartate. These findings will allow for a more rational and direct enzyme design, so that catalytic efficiency can be improved.

Acknowledgements This work was supported by the Applied Molecular Biosciences Unit—UCIBIO and Associate Laboratory i4HB, which are financed by national funds from FCT (UIDP/04378/2020, UIDB/04378/2020, and LA/P/0140/2020). RM acknowledges FCT for the PhD grant 2020.09087.BD.

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Poster #778 **online**

Going Beyond the PT2 Correlation for DSD Double Hybrids: Direct Random-Phase Approximation and Scaled MP3 Corrections

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For the revDSD [1] double hybrids, the Görling-Levy second-order perturbation theory [2] component is an Achilles' Heel when applied to systems with small band gaps (a.k.a absolute near-degeneracy correlation, type A static correlation [3]). We have explored its replacement by the direct random phase approximation (dRPA), [4] inspired by the SCS-dRPA75 functional of Kállay and coworkers. [5] The addition to the final energy of both a D4 [6,7] empirical dispersion correction, and of a semilocal correlation component, lead to significant improvements, with DSD-PBEdRPA75-D4 approaching the performance of Mardirossian and Head-Gordon's [8] ωB97M(2), and our own [1] revDSD-PBEP86-D4. This form appears to be fairly insensitive to the choice of semilocal functional, but does exhibit stronger basis set sensitivity than the PT2-based double hybrids (due to much larger prefactors for the nonlocal correlation). As an alternative, we explored adding an MP3-like correction term (in a medium-sized basis set) to both global [1] and range-separated [9] DSD-PBEP86-D4 double hybrid. These DSD3 and ωDSD3 functionals, respectively, turned out to have significantly improved the WTMAD2 (weighted mean absolute deviation [10]) for the large and chemically diverse GMTKN55 benchmark suite [10]; the added computational cost can be mitigated through density fitting techniques. The range separated ωDSD3-PBEP86-D4 (WTMAD2=1.76 kcal/mol) is the best fifth-rung [11] functional available to date.

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Poster #804 **online**

A Systematic QM/MM Study for Predicting 31P NMR Chemical Shifts for Nucleotides in Solution and Protein Environment

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Co-author/s: Johannes C. B. Dietschreit, Christian Ochsenfeld

NMR spectroscopy is a powerful tool to obtain rich structural information on extended biological systems and protein dynamics. In order to allow for reliable assignments of experimental spectra, theoretical calculations are often crucial. However, the computation of chemical shifts is very sensitive with regards to structural changes and heavily requires to account for ensemble averages. Therefore, careful selection of representative input structures is essential. With a nuclear spin of 1⁄2 and 100% natural sotopic abundance, 31P is an easily observable NMR nucleus. Because of its presence in nucleic acids and other biological systems, quantum-chemical computations of 31P NMR shielding tensors have proven to be of major importance. As an example of a biologically relevant system is the p97 ATPase, where point mutations lead to degenerative diseases in humans. By computing high quality 31P NMR chemical shifts inside the binding pocket of p97 ATPase, as well as for ADP and ATP nucleotides in solution, we aim to make a relevant contribution for understanding the mechanochemical cycle of the protein. Our methodology is based on MM-MD sampling, followed by QM/MM calculations of NMR chemical shifts. To account for conformational diversity and different interactions with the solvent, we compute the NMR shieldings as averages over the MM trajectory. Evenly spaced snapshots were extracted from the resulting trajectories and QM/MM NMR calculations were carried out at the B97-2/pcSseg-2 level of theory.

The quantum-chemically computed shieldings form broad distributions due to the structural ensemble diversity, however, due to deficiencies in the underlying MM structures, reliable assignments and links to the experiment are not possible. An intermediate step of refining the nucleotide geometries by QM/MM optimization before the NMR shift calculations leads to reasonable agreement between computation and measurement, and is therefore crucial. We applied the outlined protocol to p97 and carried out calculations inside the binding pocket. The first results show similar trends to what we have seen in solution and our results are in good agreement with the experimentally measured values.

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Poster #814 **online**

Development and Application of the Nonbonded Cationic Dummy Model Accounting for Ion-Induced Dipole Interactions

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Co-author/s: Qinghua Liao

Modeling metalloproteins often requires classical molecular dynamics (MD) simulations in order to capture their relevant motions, which in turn necessitates reliable descriptions of the metal centers involved. One of the most successful approaches to date is provided by the "cationic dummy model", where the positive charge of the metal ion is transferred toward dummy particles that are bonded to the central metal ion in a predefined coordination geometry. While this approach allows for ligand exchange, and captures the correct electrostatics as demonstrated for different divalent metal ions, current dummy models neglect ion-induced dipole interactions. Previously, we resolved this weakness by taking advantage of the recently introduced 12–6–4 type Lennard-Jones potential to include ion-induced dipole interactions for Mg2+, Al3+, Fe3+ and Cr3+. In this present study, the same strategy is extended for other divalent metal ions with more water models. Finally, the effectiveness of our new models is demonstrated in MD simulations of several diverse metalloproteins.

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Poster #819 **online**

Targeting Purine Nucleoside Phosphorylase for T-Cell-Mediated Diseases by Newly Designed Acyclovir Analogs: Combined Density Functional, Molecular Docking, and Molecular Dynamics Study

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Purine nucleoside phosphorylase (PNP) is one of the key enzymes responsible for the nucleosides and deoxynucleosides, important steps for the purine catabolism pathway. Due to having a genetic disorder, lack of PNP activity causes the loss of T-cells, and thereby, PNP inhibitors are used as a potent immunological modulator to treat autoimmune diseases, leukemia, psoriasis, rheumatoid arthritis, and Crohn's disease. Regarding this concern, herein we reported the structure-based design of some new acyclovir analogs targeting human purine nucleoside phosphorylase PNP. Herein, we apply density functional theory (DFT) to optimize at the B3LYP/6-31G(d, p) level of theory of our designed new acyclovir analogs. Dipole moment, electronic energy, enthalpy, Gibbs free energy, HOMO-LUMO gap, and softness of these modified drugs are investigated. Molecular interactions and binding energies between modified analogs and PNP were calculated and analyzed by using a series of molecular modeling techniques including Molecular Docking, MM-GBSA, Drug Likeness test, ADME/T analysis, and Molecular Dynamics Simulations. DFT analysis concluded that reduced HOMO-LUMO gap in modified analogs promotes the softness, making them relatively more polarizable than the unmodified acyclovir. Molecular docking and MD simulation revealed that modified analogs are more active than the parent, where non-covalent interactions with the residues like ASN243, SER220, ALA116, GLU201, HIS86 play important roles in ligand-protein interactions. Moreover, the Drug likeness test and ADME/T analysis suggested that modified analogs have druggable properties, are less toxic, and processed improved pharmacokinetic profiles than the parent drug. These results further confirmed the ability of modified acyclovir derivatives to bind simultaneously to the active sites of PNP and support them as potential candidates for future drug development against, respectively, T-cell-mediated diseases.

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Poster #829 **online**

Adaptive Seeding Strategies to Speed up Protein Dynamics Estimation

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The accuracy of simulated timescales of protein dynamics is limited due to sampling limitations of the rare transition events. Adaptive seeding strategies allow to preferentially sample desired areas of the landscape, allowing to reach higher accuracy with lower computational resources. The convergence of kinetic estimates is confirmed by comparison to reference plain MD simulations. Further, the upper limits for sampling performance, and scaling of adaptive seeding strategies are considered

Poster #846 **online**

Solvent Dependent Activity of Candida Antarctica Lipase B and its Correlation with a Regioselective Mono Aza-Michael Addition- Experimental and Molecular Dynamics Simulation Studies

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With the aim of gaining understanding of the molecular basis of Candida antarctica lipase B (CALB) catalyzed regioselective mono aza-Michael addition of Benzhydrazide to Diethyl maleat we decided to carry out molecular dynamics (MD) simulation studies in parallel with our experimental study. We found a correlation between the activity of CALB and the choice of solvent. Our study showed that solvent affects the performance of the enzyme due to the binding of solvent molecules to the enzyme active site region, and the solvation energy of substrates in the different solvents. We also found that CALB is only active in nonpolar solvent (i.e. Hexane), and therefore we investigated the influence of Hexane on the catalytic activity of CALB for the reaction.

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Poster #857 **online**

Computational Study of the Monoamine Oxidase B Mechanism-Based Irreversible Inhibitors

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Monoamine oxidase B (MAO B) is a flavoenzyme responsible for the metabolism of endogenic and exogenic amines such as monoamine neurotransmitters whose disturbed homeostasis is implicated in the wide range of neurodegenerative pathogenesis. MAO B represents primary pharmacological target for the treatment of the Alzheimer's and Parkinson's disease. Commercial drugs, selegiline and rasagiline, are administrated with dietary restrictions and in high doses are associated with more frequent and greater intensity side effects. [1] There is a constant market pressure for the development of new, mechanism-based MAO B inhibitors with more favourable pharmacokinetic profiles.

Innovative approach was developed for the drug design which involves binding of the scaffolds [2] with propagylamine core which is present in commerical drugs which target MAO enzymes. [3] More favourable thermodynamic profiles are obtained using methods of script based molecular docking and molecular dynamics simulations, while the kinetic profile of the inhibitory activity will be characterized via the quantum chemical cluster approach.

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Poster #885 **online**

Resolution Transformation of Coarse-Grained to Atomistic Models - From Traditional Approaches to Modern Machine Learning Techniques

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Sequential multiscale molecular dynamics simulations benefit from switching between different levels of resolution of the molecular representation, allowing us to study processes over longer timescales and simultaneously recover atomistic details. While coarse-graining is straightforward, the reverse transformation from low to high resolution, also termed backmapping, is a non-trivial task. This is mainly due to the information loss about the atomistic structure underlying the coarse-grained representation, which must be reintroduced. Here, we analyze the strengths and drawbacks of state-of-the-art backmapping methods such as fragment-based and geometric approaches, and discuss emerging modern machine learning techniques for resolution transformation. Additionally, we illustrate our ideas of an efficient artificial intelligence framework and detail the improvements we expect over current backmapping algorithms.

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Poster #893 **online**

Structural and Functional Analysis of Macromolecules based on Simulations of Small Molecular Probes

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Most enzyme structures comprise pores, channels, cavities, and pockets which pay crucial role to their architecture functionality and performance. AQUA-DUCT allows to track and calculate local distribution of small molecules inside proteins. AQUA-DUCT is a universal tool for analysis of macromolecules integral interior with access to detailed information on the transportation and enzymes binding preferences of ligands, solvents and ions. It also informs about residues controlling access to the active site and regions in which small molecules are stuck or trapped. AQUA-DUCT is independent from the system and tracked molecules, and can be applied for analysis of co-solvent MD of macromolecules in heterogenic systems.

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Poster #894 **online**

PatcHwork: A User-Friendly pH Sensitivity Analysis Web Server for Protein Sequences and Structures

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pH regulates protein function and interactions by altering the charge of individual residues causing loss or gain of intra-molecular non-covalent bonds, which may lead to structural rearrangements. While tools to analyze residue-specific charge distribution of proteins at a given pH exist, currently no tool is available to investigate non-covalent bond changes at two different pH values. To make the protein pH sensitivity analysis more accessible, we developed patcHwork, a web server that combines the identification of amino acids undergoing a charge shift with the determination of affected non-covalent bonds at two user-defined pH values. At the sequence-only level, patcHwork applies the Henderson-Hasselbalch equation to determine pH-sensitive residues. When the 3D protein structure is available, patcHwork can be employed to gain mechanistic understanding of the effect of pH. This is achieved using the PDB2PQR and PROPKA tools and non-covalent bond determination algorithms. A user-friendly interface allows visualizing pH-sensitive residues, affected salt bridges, hydrogen bonds and aromatic (pi-pi and cation-pi) interactions. patcHwork can be used to identify patches, a new concept we propose of pH-sensitive residues in close proximity on the protein, which may have a major impact on function. We demonstrate the attractiveness of patcHwork studying experimentally investigated pH-sensitive proteins. (Access: https://patchwork.biologie.uni-freiburg.de/)

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Poster #897 **online**

Molecular Dynamics Based Analyses of the Structural Impacts of Y429C Mutation on PAK1 in Neurodevelopmental Disorder

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Co-author/s: Md. Junaid, Syeda Samira Afrose, Aysha Siddiika

The p21 activated kinase 1 (PAK1) is a member of the group A PAK family of serine/threonine kinase. This PAK1 acts as the downstream effector molecule of Rho GTPases Cdc42 and Rac1 and accomplishes diverse biological actions including proliferation, survival, motility, cytoskeletal remodeling, etc. PAK1 has been evidenced to regulate brain size and function, thus indicating the requirements of PAK1 in proper neurodevelopment. Compatible with that, an Y429C gain-of-function missense variant has been ascertained mediating neurodevelopmental disorder characterized by different manifestations including developmental delay, intellectual disability, macrocephaly, seizures, ataxic gait, etc. That variant is identified in a five years old subject, where replacement of tyrosine with cysteine might lead to the catalytically competent state of PAK1. The aim of this study is to unveil the structural consequences of Y429C in PAK1. First of all, we have collected 3D crystal structure of protein from Protein Data Bank (www.rcsb.org) after that Molecular dynamics simulation (MDS) has been executed for a period of 500 ns at the physiological conditions. We performed an extensive analysis of RMSD, SASA, RMSF, Rg, hydrogen bond, DCCM, and PCA, which revealed a substantial conformational alteration and instability in the Y429C variant of PAK1 protein's structure. This comprehensive study will be helpful to scrutinize PAK1 mutant-mediated neurodevelopmental disorder and develop a promising treatment intervention designing novel inhibitors of activated PAK1 variant.

Poster #899 **online**

In silico Screening of Novel COX-2 Inhibitors from Marine Natural Products Against Colorectal Cancer

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Co-author/s: Md. Junaid, Aysha Siddika

Colorectal cancer (CRC) is the second major cause of death from cancer worldwide, projected to increase to 3.2 million new cases in 2040. Despite developments in early detection screening techniques and treatment strategies for late-stage and advanced metastatic carcinoma, CRC's heterogeneity makes the discovery of new therapeutic approaches of practical importance. Several clinical trials and epidemiological research have shown that inhibition of cyclooxygenase-2 (COX-2) enzymatic activity reduces the risk of CRC, particularly surgical-related metastasis and cancer recurrence. COX-2 overexpression is implicated in colorectal carcinogenesis because it mediates the biosynthesis of prostaglandin E2 (PGE2), a potent inhibitor of T lymphocyte proliferation, allowing colon cancer cells to evade host immunological defense. PGE2 also promotes CRC cells invasion, apoptosis, and most importantly, cell proliferation through the PI3K, c-Met/EFGR, and Wnt/β-catenin signaling pathways, respectively. As a result, the COX-2/PGE2 pathway is considered to be a critical and viable target in CRC therapy. This study aims at screening for potent and novel COX-2 inhibitors from marine natural products (MNPs), which have been reported to have anti-CRC properties. After optimization of the compounds, they were docked "site specific rigid and flexible docking" using AutoDock Vina against the COX-2 receptor-binding sites, which demonstrated multiple MNPs having strong binding interactions with important residues of COX-2, like Tyr385, Ser530, Arg120, and His90. To further validate the selected compounds with the highest binding affnity, molecular dynamics simulation was also performed using GROMACS software to study their binding mechanisms, flexibility and structural behavior. Additionally, ADME/T analysis of the selected compound also revealed its impressive properties as a lead molecule. Therefore, these results propose a potent COX-2 inhibitor that must be further investigated using cell lines and animal models to serve as part of the CRC therapeutics.

Poster #900 **online**

Structure-Based Drug Design by Targeting CHEK1 from Potent Natural Products against Colorectal Cancer

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Co-author/s: Md. Junaid

Cancer is one of the prominent causes of death worldwide, and Colorectal cancer (CRC) is one of the most prevalent in developed countries rather than developing countries. The estimated growth of CRC incidents will be 25 million by 2035. Thorough research and analysis established the positive correlation between CRC and CHEK1. Overexpression of CHEK1 was found in the CRC incidents where CHEK1 mediated DNA damage repair prevents apoptosis of the cancerous cells. Thus, CHEK1 inhibition prevents cancerous growth of the CRC cells. As a result, CHEK1 stands as a suitable target for developing drugs against it. Here in this study, we performed virtual screening and screened the natural plant-derived compound library against CHEK1. After that, best candidates from virtual screening undergoes in molecular dynamic simulation for investigate their binding mechanism as well stability. Our investigation revealed that some of these natural compounds strongly bind with CHEK1 active site critical residues-Leu84, Glu85, Tyr86, Cys87, and Asp148. Furthermore, pharmacokinetic profiling, drug-likeness, and toxicity analyses enabled us to choose the best hits against CHEK1. From the findings it is revealed that natural products can be potentially excellent therapeutic options against CRC.