COMPUTER SIMULATION AND THEORY OF MACROMOLECULES

Hünfeld, April 28-29, 2023, Hybrid

Section 1:

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oral #92 **on-site**

Maximum Entropy Force Field Refinement

Presenting author: **Benjamin Eltzner**

Max Planck Institute for Multidisciplinary Sciences, Theoretical and Computational Biophysics, Computational Biomolecular Dynamics, Göttingen, Germany

Co-author/s: Bert L. de Groot, Michael Habeck

In some cases, features measured from a protein ensemble, like atom distances, are not recovered on average in molecular dynamics simulations. To remedy this problem, various ensemble refinement methods have been developed. We approach the problem from the maximum entropy point of view, which pursues the conceptually compelling goal to determine a least biased force field modification for a specific system. The problem then presents as a doubly intractable Bayesian inference problem and thus requires sophisticated two-step Monte Carlo methods. This approach goes beyond typical ensemble refinement approaches by providing a system specific force field refinement and variance estimates for force coefficients. In future work, we will aim to determine general force field parameters based on the system specific force estimates.

oral #112 **on-site**

Towards Markov State Models of Chemically Driven Non-Equilibrium Steady States

Presenting author: **Emanuele Zippo**

Johannes Gutenberg University, Department of Physics, KOMET1, Mainz, Germany

Co-author/s: Lukas Stelzl

Non equilibrium steady states (NESS) are a fundamental concept in biophysics, as many biological systems operate far from thermodynamic equilibrium, driven by external forces or internal gradients. An example of chemically driven NESS can be the system composed of an enzyme and a substrate that can be converted into product by burning some chemical fuel. In this work, we investigate the effect of phosphorylation on an aggregate of TDP-43 (a protein with an intrinsically disordered domain) operated by the enzyme Casein Kinase 1 delta (CK1δ), using coarse-grained implicit solvent molecular dynamics simulations. We face the problem of simulating chemical reactions using Monte Carlo steps. This system also has biological relevance as TDP-43 aggregates may play a role in the development of neurodegenerative diseases, such as ALS, FTD or Alzheimer's disease.

We also focus on the use of Markov state models (MSMs) in non-equilibrium processes. MSMs are a powerful tool for studying complex dynamics, as they need only information about local equilibrium within conformational macro-states to compute transition rates. Our aim is to build MSMs from simulation trajectories in order to get a coarse-graining in time and an interpretable representation of the dynamics of our system.

oral #174 **on-site**

Clustering Molecular Dynamics Trajectories Using Density and Flux

Presenting author: **Jayashrita Debnath**

Max Planck Institute of Biophysics, Theoretical Biophysics, Frankfurt am Main, Germany

Co-author/s: Gerhard Hummer

Molecular dynamics (MD) simulations are a powerful tool for studying a wide range of molecular systems and processes, with applications ranging from materials science to biology and medicine. Analyzing these simulations often involves finding a low-dimensional representation of the trajectory data and clustering the sampled configurations into kinetically relevant metastable states. The steady growth in the time and length scales of MD simulations, and in the complexity of their molecular systems, necessitates the development of new analysis tools that do not rely entirely on chemical or physical intuition. Here, we propose a neural network based unsupervised algorithm that can identify states using the static and dynamic information encoded in the trajectories. The network identifies metastable states by modeling a probability distribution of the data in a reduced dimensional space and learns the state boundaries by minimizing the flux between states. Furthermore, it can learn the optimal number of states from single long equilibrium trajectories or multiple short ones. After demonstrating the effectiveness of this method for a toy potential, we apply it to trypsin-benzamidine unbinding as a model of drug binding kinetics, to and folding-unfolding transitions of the villin headpiece subdomain.

oral #181 **on-site**

Scrutinizing the Protein Hydration Shell from MD Simulations against Experimental Solution Scattering Data: Effects of Water Models, Force Fields, and Surface Compositions

Presenting author: **Johanna-Barbara Linse**

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

Co-author/s: Jochen S. Hub

The hydration shell of proteins plays key roles in protein stability, folding, recognition, and enzyme activity. Water in crowded biological cells is largely hydration shell water. However, it remained unclear whether the hydration shell predicted by explicit-solvent molecular dynamics (MD) simulations matches experimental conditions, while accurate experimental probes of the hydration shell structure remained limited. Small-angle scattering (SAS) in solution using X-rays (SAXS) or neutrons (SANS) in principle provides 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 bulk solvent. Using MD simulations and explicit-solvent SAXS/SANS calculations, we computed Rg and I0 for five different proteins and a set of 18 different combinations of protein force fields and water models, and we validated the simulation results against consensus data from a recent worldwide round robin benchmark [1]. Overall, we find remarkable agreement between MD simulations and consensus SAS data, however the agreement is force field-dependent. Certain force field/water model combinations underestimate the hydration layer contrast significantly, while water models with increased dispersion interactions may, for some proteins, overestimate the hydration layer contrast. In addition, we performed simulations of a GB3 domain with mutations of surface amino acids (AA) for three different water models, revealing that the hydration layer effect on Rg and I0 depends on the surface AAs. To quantify how the surface AAs affects the hydration layer, we present a proteins hydration shell contrast score for the 20 most common amino acids. Our studies show that explicit-solvent SAS calculation and consensus SAS data provide a novel route for scrutinizing the hydration layer of proteins and with the amino acids score a powerful tool for the prediction the influence of protein hydration layers on Rg and I0 has been established.

[1] A Round Robin Approach Provides a Detailed Assessment of Biomolecular Small- Angle Scattering Data Reproducibility and Yields Consensus Curves for Benchmarking. Trewhella, J., Vachette, P., Bierma, J., Blanchet, C., Brookes, E., Chakravarthy, S., Chatzimagas, L., Cleveland, T.E., Cowieson, N., Crossett, B. et al., (2022), Acta. Cryst. D78, https://doi.org/10.1107/S2059798322009184

oral #201 **on-site**

The Influence of Lipid Composition on the Free Energy of Membrane Pore Formation

Presenting author: **Leonhard Starke**

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

Co-author/s: Jochen S. Hub

Biological membranes exhibit highly heterogeneous lipid composition, comprising hundreds or even thousands of different chemical species. Given that membranes act as barriers between cells, an important question is how this complexity affects the membrane's mechanical properties and its resistance against the formation of an aqueous defects. We calculated free energy profiles of pore nucleation and expansion for a large set of biologically relevant complex membranes using our in-house developed reaction coordinate [1]. The systems containing up to 14 lipid types reveal large variations in their free energy profiles, which likely reflect their biological functions. For instance, the plasma membrane with its rich sterol content are by far more stable as compared to membranes of intracellular compartments. To rationalize the variations in membrane stability by their lipid content, we calculated pore free energies for 17 model membranes with varying sterol content, tail length, tail unsaturation, or head group type, revealing strong dependence of membrane stability on the lipid properties.

[1] Joint Reaction Coordinate for Computing the Free-Energy Landscape of Pore Nucleation and Pore Expansion in Lipid Membranes, Hub J. , J. Chem. Theory Comput. 2021, 17,1229-1239

oral #263 **on-site**

Engineering PET-Degrading Enzymes – Targeting the Energy Barrier for PET Binding

Presenting author: **Anna Jäckering**

Research Center Jülich, Institute of Biological Information Processing 7 - Structural Biochemistry, Computational Biochemistry Group, Jülich, Germany

Co-author/s: Birgit Strodel

In view of the worsening climate crisis and increasing plastic waste pollution, scientific interest in the development of an environmentally friendly enzymatic degradation mechanism for plastics is growing. However, the bottleneck in the industrial application of enzymes for plastic waste recycling is their insufficient activity and partial lack of stability under industrial conditions. To this end, we investigated the binding behavior of highly active PET-degrading enzymes to polyethylene terephthalate (PET). Adsorption to the PET surface could be captured by classical molecular dynamics (MD) simulations. However, the entry of PET into the active site associated with the formation of productive binding poses was presumably hindered by an energy barrier limiting the activity of the enzyme. Using Hamiltonian Replica Exchange MD (HREMD) simulations, we were able to overcome this barrier and investigate entry pathways leading to productive conformations. In addition to hindering intramolecular PET interactions, we identified amino acids that potentially hinder entry into the binding site based on free energy surface profiles of amino acid-PET interaction. These residues serve as promising mutation sites to enhance PET degradation activity, which will be investigated in vitro in the future.

oral #278 **on-site**

Automated and Systematic Derivation of Parameter Type Definitions for Molecular Mechanics Force Fields

Presenting author: **Tobias Hüfner**

Max Planck Institute of Biophysics, Theoretical Biophysics, Frankfurt am Main, Germany

Co-author/s: Michael K. Gilson, Gerhard Hummer

Molecular Mechanics force fields are of high relevance in various areas of chemistry, physics and biology. They require a large number of parameters, which are typically derived from quantum chemistry calculations and tuned to enable simulations to replicate experimental observables, e.g. properties of pure liquids, as well as quantum mechanical observables, e.g. energy profiles of rotatable bonds. In these force fields, a given parameter is always associated with a specific force type (e.g. bond stretching) and consists of (A) one or more numerical values specific for that force type and (B) a parameter type definition that enables the assignment of this parameter to specific atoms in the molecule via a chemical perception strategy (e.g. using atom types or SMARTS specifiers). While their numerical values can be straightforwardly optimized using numerical solvers, the parameter type definitions typically remain constant during the optimization process. For obvious reasons, force fields must contain as few parameters as possible while still accurately capturing the physics of the molecules. The choice as to which parameter type definition to include in the force field is usually made by a human with domain knowledge, however this limits the extensibility and transferability of the force field. Also, these choices are mostly made on an ad hoc basis since one can hardly evaluate the sensitivity of a force field with respect to each possible variation of parameter type definitions. For instance, it seems intuitively correct to assign distinct force field parameters to amide and ester structures, however it is not clear whether assigning them distinct parameters is actually justified by a reasonable improvement in force field accuracy with respect to high-level (or experimental) reference data.

In this contribution, we derive parameter type definitions alongside their parameter values from scratch using standard high-level reference data. Furthermore, we demonstrate how the posterior distribution of parameter type definitions can be sampled in an efficient way, thus allowing for the assessment of degeneracy and uncertainty in the space of parameter type definitions. Our approach does not require ad hoc human domain chemistry knowledge, like hand-drawn definitions of functional groups, thus enables a truly systematic and automated fitting of molecular mechanics force fields. In order to guide the search for parameter type definitions we leverage parameter gradients, which we currently limit to valence potential energy functions. We will demonstrate the validity of our approach using small molecule datasets of varying complexity and give an outlook for the derivation of force fields for drug-like molecules.

oral #289 **on-site**

Coarse-Grained Modeling of DNA Origami Structures Using oxDNA

Presenting author: **Erik Poppleton**

Max Planck Institute for Medical Research, Heidelberg Institute for Theoretical Studies (HITS), Biophysical Engineering, Molecular Biomechanics, Heidelberg, Germany

Co-author/s: Michael Matthies, Joakim Bohlin, Jonah Procyk, Mathias Centola, Michael Famulok, Lorenzo Rovigatti, Petr Šulc

The oxDNA model is a popular one-bead-per-residue coarse grained model used to model biophysical properties of large DNA structures. The model has been shown to reproduce the structural, mechanical, and dynamic properties of both single stranded and double stranded DNA. The model is particularly well-suited to the study of DNA origmi nanostructures, designed structures which leverage the base-pairing of DNA to self-assemble defined architectures with nanoscale resolution. Here, I will discuss the recent developments in the oxDNA software ecosystem including a newly optimized codebase, a Python analysis library, and a web-based visualization and editing tool. I will also discuss the application of the model to analysis of the mechanical properties of a leaf-spring nanoengine.

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oral #294 **on-site**

Mechanisms of Ribosome Stalling and Unstalling Studied by MD Simulations

Presenting author: **Lars V. Bock**

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

Co-author/s: Helmut Grubmüller

The reasons for ribosomes being stalled in certain conformational states are manifold. For example, many bound antibiotics impede the conformational changes necessary for progression thereby trapping the ribosome in a specific state. The stalled conformations can lead to homogeneous ensembles and are therefore especially accessible to structure determination by cryo-EM and X-ray crystallography.

To address mechanisms of stalling, we use all-atom Molecular Dynamics simulations of the stalled structures (e.g., including the antibiotic) and of structures after in-silico removal of the cause for stalling (e.g. removing the antibiotic or introducing a mutation). The comparison of the acquired ensembles allows us to formulate hypotheses of the atomistic mechanism, which can then be tested in experiments.

In collaborations with experimental groups, we identified the stalling mechanism of Erm leader peptides in the presence of macrolide antibiotics that induces the expression of a downstream macrolide resistance determinant. Further, we found how the antibiotic kirromycin sterically blocks a conformational change of EF-Tu necessary for EF-Tu dissociation after GTP hydrolysis. mRNAs which lack a stop codon result in ribosomes stalled at the 3' end of the mRNA. Alternative ribosome-rescue factor B (ArfB) rescues stalled ribosomes by tRNA-peptide hydrolysis, thus releasing the peptide. ArfB consists of an N-terminal domain with the GGQ motif required for the hydrolysis, a C-terminal domain which acts as a sensor for the empty mRNA entry channel, and a linker connecting the domains. In simulations of wild-type ArfB, we found an alpha helix (residues 80-99) stabilizing the tRNA CCA-tail in a hydrolysis-competent conformation. Cutting the linker, or introducing mutations of conserved linker residues results in a shifted helix and consequently different CCA-tail conformations. We suggest that the placement of the C-terminal domain in the empty mRNA entry channel determines the position of the linker which, in turn, restricts the conformation of the alpha helix and stabilizes the tRNA in a hydrolysis-competent conformation.

oral #296 **on-site**

Size-dependent Sedimentation of Nanocrystals: The Role of the Ligand Shell Structure

Presenting author: **Debora Monego**

Heidelberg Institute for Theoretical Studies (HITS), Molecular Biomechanics, Heidelberg, Germany

Co-author/s: Stefano Bernardi and Asaph Widmer-Cooper (University of Sydney, Australia)

The chemical, electronic, optical, magnetic and catalytic properties, as well as the self-assembly of hybrid inorganic-organic core-shell nanoparticles depend strongly on their size and composition. Hence, there is a pressing need for a reliable method that can provide full characterisation of these particles. Although transmission electron microscopy (TEM) provides high-resolution detail of a particle's size, shape, and structure, discerning the organic materials bound on the nanocrystal surface is still a challenge due to low atomic contrast. Yet, parameters related to the overall hybrid particle (inorganic core and organic shell) properties influence particles' solubility, electronic properties, assembly and reactivity. In this context, analytical ultracentrifugation (AUC) appears as an alternative to characterise these particles in solution, being sensitive to changes in the density and size of both core and shell components of nanoparticles. We use molecular dynamics simulations (MD) to test the validity of the Stokes-Einstein-Sutherland (SES) equation for systems of CdSe quantum dots coated with alkanethiol ligands in chloroform and explain inconsistencies between the sedimentation trends observed in AUC experiments and the ones predicted for these particles in a Stokes flow. We find that varying the size of the particle changes the structure of the ligand shell and the way it interacts with the solvent and will dictate the diffusion and sedimentation behaviours of the nanocrystals.

oral #326 **on-site**

Grid-Based State Space Exploration for Molecular Binding

Presenting author: **Hana Zupan**

Free University of Berlin, Institute for Chemistry and Biochemistry, Molecular Dynamics, Berlin, Germany

Co-author/s: Frederick Heinz, Bettina Keller

Binding processes are difficult to sample with molecular-dynamics (MD) simulations. In particular, the state space exploration is often incomplete. Evaluating the molecular interaction energy on a grid circumvents this problem but is heavily limited by state space dimensionality. Here, we make the first steps towards a low-dimensional grid-based model of molecular binding. We discretise the state space of relative positions and orientations of the two molecules under the rigid body assumption. The corresponding program is published as the Python package molgri. For the rotational component of the grids, we test algorithms based on Euler angles, polyhedra and quaternions, of which the polyhedra-based are the most uniform. The program outputs a sequence of molecular structures that can be easily processed by standard MD programs to calculate grid point energies. We demonstrate the grid-based approach on two molecular systems: a water dimer and a coiled-coil protein interacting with a chloride anion. For the second system we relax the rigid-body assumption and improve the accuracy of the grid point energies by an energy minimisation. In both cases, oriented bonding patterns and energies confirm expectations from chemical intuition and MD simulations. We also demonstrate how analysis of energy contributions on a grid can be performed and demonstrate that electrostatically-driven association is sufficiently resolved by point-energy calculations. Overall, grid-based models of molecular binding are potentially a powerful complement to molecular sampling approaches, and we see the potential to expand the method to quantum chemistry and flexible docking applications.

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oral #327 **on-site**

Effect of Selectivity Filter Mutations on K+ Permeation Mechanism in the KcsA Channel: A Molecular Dynamics Study

Presenting author: **Andrei Mironenko**

Max Planck Institute for Multidisciplinary Sciences, Theoretical and Computational Biophysics, Computational Biomolecular Dynamics, Göttingen, Germany

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

K+ channels are known for combining high conductivity with high ion selectivity. To explain such efficiency, two permeation mechanisms were proposed, each supported by certain experimental and computational data. The 'direct knock-on' mechanism is defined by water-free ion permeation and formation of direct ion-ion contacts in the narrowest part of K+ channels - selectivity filter (SF) - that lead to high permeation rates and intrinsic ion selectivity. Another mechanism, formulated originally for K+ channels, 'soft knock-on', involves separation of K+ by water molecules in the SF and water co-permeation. Recently, X-ray structures of two SF mutants of the KcsA channel - G77A and T75A - were published. The arrangements of K+ and water in their SFs were similar to the two canonical soft knock-on configurations. It was then suggested that those mutants isolate the actual configurations that occur during permeation in the WT KcsA, thus arguably presenting proof of the soft knock-on mechanism in WT. Here, we use MD simulations to study how G77A and T75A mutations affect ion permeation in KcsA. We show that, while a strictly water-free direct knock-on permeation is observed in WT, conformational changes in SF induced by these mutations lead to a very different mechanism characterized by co-permeation of K+ and water. At the same time, both mutations drastically reduced conductance and impaired K+/Na+ selectivity, thus suggesting the importance of full dehydration of K+ (direct knock-on mechanism) for the hallmark high conductance and high selectivity of K+ channels. In general, we present a case where mutations introduced at the critical points of the permeation pathway in an ion channel drastically change its permeation mechanism in a non-intuitive manner.

oral #344 **on-site**

A Minimal Markov Model for Rotary Catalysis of F1-ATPase

Presenting author: **Yixin Chen**

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

Co-author/s: Helmut Grubmüller

F1-ATPase, the soluble part of the F-ATP synthase, is an ATP-driven rotary molecular motor. Whereas the fundamental idea of the mechanism of F1-ATPase, known as rotary catalysis, is widely accepted, there is still no consensus on the precise catalytic pathway, thermodynamics and kinetics. Here we aim at a minimal, unified and thermodynamically consistent model that quantitatively explains four essential aspects of F1-ATPase function, namely, [ATP]-dependent turnover, near 100% chemo-mechanical coupling efficiency, nucleotide titration curves, and rotation kinetics.

To this end, we formulated a generic Markov model which incorporates only a few essential degrees of freedom (DOF) such as several β-subunit conformations and discrete orientations of the γ-subunit. A few alternative assumptions about the DOFs lead to a limited number of variants of the generic model. To select those variant(s) that best agree with available experimental observations, we first trained each variant using a Bayes approach and the experimental data of turnover, efficiency and titration curves. Those variants whose training succeeded were subsequently cross-validated against measured rotation kinetics.

Only one variant agreed with all available experimental data, which we propose as a minimal working model for the rotary catalysis of F1-ATPase. This model reconciles the decade-long bi-site vs. tri-site controversy and assigns crystal structures to defined stages of the catalytic cycle. Unexpectedly, within the framework of our model, at least four conformations of the β-subunits are required to fully account for all experimental data. Interaction between the γ- and β-subunits, modeled as a selection of the β-subunit conformations by the orientation of the γ-subunit, is shown to play an essential role in explaining the experimental data.

oral #363 **on-site**

Incorporating Chemistry Into Classical Molecular Dynamics Simulations by Machine Learning

Presenting author: **Frauke Gräter**

Heidelberg Institute for Theoretical Studies (HITS), Molecular Biomechanics, Heidelberg, Germany

Co-author/s:

Proteins are inherently reactive. Among others, mechanical force can trigger bond scission and a variety of downstream chemical reactions in proteins. I will present our newly developed hybrid kinetic Monte Carlo / Molecular Dynamics (KIMMDY) scheme that incorporates chemical reactions into classical molecular simulations in a highly efficient and yet accurate manner. KIMMDY makes use of reaction barriers predicted by graph neural networks which were trained on thousands of pre-computed barriers and chooses reactions to occur among the jiggling and wiggling of the protein or protein material.

Using KIMMDY, we predict the mechanochemistry – as of now chemical bond scissions and hydrogen atom transfer reactions – within stretched collagen, the most abundant protein of our body. Our scale-bridging ML-enhanced simulation technique is applicable to complex – biological as well as synthetic – molecules and materials and can be extended to other chemistries.

[1] Zapp et al, Nat Comm, 2020

[2] Rennekamp et al, JCTC, 2020

[3] Riedmiller et al, ChemRxiv, 2023

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oral #404 **on-site**

Protein Dynamics in a Biomolecular Condensate

Presenting author: **Miloš Ivanović**

University of Zurich, Biochemistry Department, Molecular Biophysics, Zurich, Switzerland

Co-author/s: Nicola Galvanetto, Aritra Chowdhury, Andrea Sottini, Mark Nüesch, Daniel Nettels, Robert B. Best, Benjamin Schuler

Proteins and nucleic acids can phase-separate in the cell to form concentrated biomolecular condensates. Their functions span many length scales: Condensates modulate interactions and chemical reactions at the molecular scale, organize biochemical processes at the mesoscale, and compartmentalize cells. Understanding the underlying mechanisms requires detailed knowledge of the rich dynamics across these scales. The mesoscopic dynamics of biomolecular condensates have been extensively characterized, but the behavior at the molecular scale has remained more elusive.

Here, as an example of biomolecular phase separation, we study coacervates of two highly and oppositely charged disordered human proteins [1] - linker histone H1 and its nuclear chaperone prothymosin-α [2,3]. Their dense phase is 1000 times more concentrated than the dilute phase, and the resulting percolated interaction network leads to a bulk viscosity 300 times greater than that of water. However, single-molecule spectroscopy reveals that at the molecular scale, the disordered proteins remain exceedingly dynamic, with their chain configurations interconverting on sub-microsecond timescales. Microseconds long large-scale all-atom explicit-solvent molecular dynamics simulations (~200 proteins, ~4 million atoms) reproduce the experimental observations and explain this apparent discrepancy: They reveal that the underlying interactions between individual side chains are remarkably short-lived and exchange on a pico- to nanosecond timescale. Our results suggest that local biomolecular rearrangements required for efficient reactions at the molecular scale can remain rapid despite the high global viscosity of phase-separated systems.

[1] Galvanetto *, Ivanović *, Chowdhury, Sottini, Nüesch, Nettels, Best, Schuler, "Ultrafast molecular dynamics observed within a dense protein condensate", bioRxiv, https://doi.org/10.1101/2022.12.12.520135 (2022)

[2] Borgia *, Borgia *, Bugge *, Kissling, Heidarsson, Fernandes, Sottini, Soranno, Buholzer, Nettels, Kragelund, Best, Schuler, “Extreme disorder in an ultra-high-affinity protein complex,” Nature 555, 61–66 (2018)

[3] Heidarsson *, Mercadante *, Sottini, Nettels, Borgia, Borgia, Kilic, Fierz, Best, Schuler, "Release of linker histone from the nucleosome driven by polyelectrolyte competition with a disordered protein", Nat. Chem. 14, 224-231 (2022)

oral #457 **on-site**

Pathways of Dimerization of STIM1 Transmembrane Helices

Presenting author: **Ferdinand Horvath**

Johannes Kepler University, Department for Theoretical Biophysics, Linz, Austria

Co-author/s: Hendrik Jung, Thomas Renger, Gerhard Hummer

STIM1 is a Ca2+-concentration sensing protein situated in the endoplasmic reticulum (ER) membrane. When ER Ca2+ stores are depleted, STIM1 undergoes a large-scale conformational transition, which proceeds from the dimerization of its transmembrane (TM) domain. We use the aimmd algorithm, which combines transition path sampling with machine learning, to exhaustively sample the dimerization of STIM1-TM helices in all-atom molecular dynamics simulations. Our algorithm autonomously initiates simulations from different starting configurations x and probes whether STIM1-TM separates or dimerizes. This allows us to both sample the transition path ensemble and to train a model of the probability of dimerization p(x). We find that STIM1 dimerizes in three distinct configurations, with the dominant bound state centering around contacts supported by the SxxxG TM interfacial motif. Our model reveals that not all interhelical contacts are conductive for imerzation, with some contacts already forming at the midpoint of the dimerization transition, when p(x) = 0.5. We provide detailed atomistic insight into how STIM1-TM helices associate along different dimerization pathways, displacing intervening lipids, forming interhelical contacts and finally settling into a bound configuration.

oral #477 **on-site**

Residue-Specific Protein-Cosolvent Interactions in All-Atom and Coarse-Grained MD Simulations

Presenting author: **Tobias Marcel Prass**

Ruhr University, Theoretical Chemistry, Molecular Simulation, Bochum, Germany

Co-author/s: Lars V. Schäfer

Therapeutic monoclonal antibodies are often administered at very high concentrations. Protein stability and solubility under these highly crowded conditions can often be improved by adding cosolvents such as L-arginine and L-glutamate. The exact molecular mechanisms by which these cosolvents work are not understood. In principle, MD simulations can provide the lacking insights into the specific interactions that are at play. However, high-concentration protein systems require large system sizes and long simulation times (on the order of many microseconds or even longer), which are not easily accessible with all-atom approaches. Here, we characterize the protein-interaction profiles of the cosolvents L-arginine and L-glutamate from extended MD simulations with three different all-atom force fields, and quantitatively compare them to the ones obtained with the Martini3 coarse-grain force field. We find distinct differences between the three all-atom force fields tested (a99SB-ILDN, C36m, and C36m with improved cation-pi interactions suggested by Chipot et al). Furthermore, we find that Martini3 provides, on average, reasonable interaction strengths between the proteins and the cosolvent molecules, but that it underestimates the residue specificity. On the basis of these results, we suggest a reparametrization strategy for protein-cosolvent interactions in Martini3, which enables more accurate predictions of protein-cosolvent interactions with coarse-grain simulations.

oral #488 **on-site**

A One-Bead-Per-Saccharide (1BPS) Model for Multiscale Modelling of the Brain ECM

Presenting author: **Saber Shakibi**

University of Groningen, Zernike Institute for Advanced Materials, Micromechanics, Groningen, The Netherlands

Co-author/s: Patrick Onck, Erik Van der Giessen

Glioblastoma is one of the most common and malignant brain tumors with a five-year survival rate of only 6%. The progression of this tumor is associated with an increase in its stiffness and remodeling of the extracellular matrix (ECM). The long-term aim of our work is to understand the relationship between this remodeling and the increased stiffness of the brain. For this we are developing a multiscale computational model of the brain ECM.

The ECM of many tissues is based on collagen, whereas the brain ECM is mainly composed of hyaluronic acid, chondroitin sulfate proteoglycans and tenascins. We used the iterative Boltzmann inversion (IBI) method to develop a one-bead-per-saccharide (1BPS) model for hyaluronic acid and chondroitin sulfates based on an existing 3-bead-per-saccharide model [1]. The correlation between the dihedral terms turned out to be essential for this coarse-graining, whereas the IBI method assumes uncorrelated interactions in the system. To remedy this, we have developed a methodology to explicitly introduce correlations between dihedrals. The coarse graining of the 1BPS model allows to make predictions that match experimental observations at length scales relevant to the brain ECM without any fitting parameters.

To model the conformation of proteoglycans, we have combined the 1BPS model with a one-bead-per-aminoacid (1BPA) model previously developed in our group [2,3] and an elastic network model for the folded sections. This model has been validated for aggrecan (a well-studied proteoglycan) in terms of radius of gyration, and is being used now for predicting the structure–property relations of brain-specific proteoglycans (i.e. brevican, neurocan and versican V2). The model for hyaluronic acid and brain-specific proteoglycans will be combined with a model at the same scale for tenascins in a network model.

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[1] M. Bathe et al., Biophys J 2005, vol. 88, no. 6, pp. 3870–3887.

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oral #543 **on-site**

Refining Active Sites of Proteins to Sub-Ångström Resolution by Combining Theoretical and Experimental Infrared Spectroscopy

Presenting author: **Katharina Leitmann**

Ruhr University, Department of Biophysics, Biomolecular Simulations, Bochum, Germany

Co-author/s: Fabian Rütten, Luca Klan, Alexander Kusch, Marvin Scherlo, Philipp Althoff, Udo Höveler, Till Rudack

Often, sub-Ångström resolution structural insights into active sites of proteins are crucial to discover the detailed structure function relationships. We have proven that such high resolution is needed to understand enzymatically catalyzed hydrolysis reaction mechanism of the small GTPases, which are crucial switches that regulate cellular processes.

Therefore, we have developed a workflow to integrate experimental and theoretical infrared (IR) spectroscopy to optimize catalytic centers of enzymes to sub-Ångström resolution. This workflow combines classical molecular mechanics (MM) simulations (Gromacs or NAMD), quantum mechanics (QM) optimizations (ORCA or Gaussian) and hybrid QM/MM simulation methods. IR spectra are either calculated through the autocorrelation function of the change of the dipole moment within a trajectory or by a frequency calculation of vibrational modes using normal mode analysis (NMA). For the latter, it is important that the conformation is a minimum structure. Therefore, we developed an iterative hybrid QM/MM strategy to obtain minimum structures.

To validate sub-Ångström resolution structural information derived from the simulation trajectories, calculated IR spectra are compared with experimental ones. Unlike experiments, simulation allows access to each transition structure. The combination of these individual structures into a trajectory makes it possible to analyse dynamic processes such as reactions. NMA is performed on selected transition structures and the resulting spectra are finally combined into a cumulative spectrum. We developed a method to extract the atomic contribution of each vibrational mode that enabled us to localize and correlate the impact of detailed structural changes in the sub-Ångström regime with our calculated spectra.

Comparing wild type and malfunctioning variants lead to insights in detailed structural changes below the resolution of structure-resolving experiments like X-ray crystallography providing structural explanations for the malfunctioning. Such explanations can e. g. assist for targeted drug design to attack malfunctioning proteins that lead to diseases.

oral #550 **on-site**

Challanges and Solution for Molecular Dynamics Simulations at the Mesoscale

Presenting author: **Bart Bruininks**

University of Helsinki, Soft Matter Physics, Biomolecular Soft Matter Physics, Helsinki, Finland

Co-author/s: Juho Liekkinen, Julius Kiuru, Ksnenia Korshunova and Ilpo Vattulainen
In collaboration with:
Tsjerk Wassenaar, Siewert Jan Marrink and Paulo CT de Souza

Using coarse grained molecular dynamics (MD), biological assemblies at mesoscale (nm<meso<µm) are becoming possible at their relevant time scales (ms). This allows for the study of for example: eukaryotic organelles, vaccine vectors, nanomaterials or viral assembly, all with molecular detail. However due to the fact that MD methods were historically designed with a single subject in mind (i.e. a protein in water, a protein in a lipid bilayer, a single dimer, etc.), these mesoscale assemblies come with many obstacles. Such challenges lie in almost any aspect involved in the MD study of said systems from producing the initial states, to running the simulation and the analysis. We will present our proceedings on tackling these aspects mainly focusing on biological examples. Topics that will be touched are Martini3 multimer Go, the required initial state building, the MD engine and high-level analysis software, all with respect to the investigation of next generation (gene) vector delivery systems.

oral #556 **on-site**

Path Separation of Dissipation-Corrected Targeted Molecular Dynamics Simulations of Protein-Ligand Unbinding

Presenting author: **Matthias Post**

University of Freiburg, Institute of Physics, Biomolecular Dynamics, Freiburg, Germany

Co-author/s: Steffen Wolf, Gerhard Stock

We present a framework to estimate reaction rates from targeted MD simulations. To enhance the sampling of an otherwise rare bio-molecular process such as the unbinding of small molecule drugs from their target proteins, a moving distance constraint is employed to enforce the transition from an initial to a final state. However, both the distribution of conformations and the time-scales associated to the transitions between them are strongly biased. By a proper reweighing by the applied constraint forces, structure-based dimensionality reduction methods can still be used to be able to find distinct reaction pathways. Then, the free energy profile and friction along the respective pathway can be estimated. Providing a path-specific Langevin model, reaction rates can be computed cost-efficiently to finally result in a global model of the bio-molecular process.

oral #558 **on-site**

Modeling the Electron Transfer Activation of European Robin Cryptochrome 4

Presenting author: **Anders Frederiksen**

Carl von Ossietzky University, Institute of Physics, Quantum Biology and Computational Physics, Oldenburg, Germany

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

The primary step in the elusive ability of migratory birds to sense weak Earth-strength magnetic fields is supposedly the light-induced formation of a long-lived, magnetically-sensitive radical pair inside a cryptochrome flavoprotein located in the retina of these birds. The radical pair is created upon blue light absorption by a flavin chromophore, triggering a series of sequential electron transfer steps across a tetradic tryptophan chain towards the flavin acceptor. In the framework of real-time QM/MM electron transfer simulations based on the DFTB approach we attempt to gain a better understanding of the electron transfer process that is essential for the birds’ ability to navigate on their migratory route.

oral #565 **on-site**

Investigating Amylose-Amylomaltase Binding with H-REMD Simulations

Presenting author: **Richard Kullmann**

Max Planck Institute of Colloids and Interfaces, Biomolecular Systems, Computational Biophysics, Potsdam, Germany

Co-author/s: Thomas Weikl, Christian Roth

Starch is a crucial component of energy supply in nature. It is made up of amylopectin and amylose which are both sparingly soluble in water. This makes the enzymes involved in the degradation of these substrates a compelling subject of study. One of these is Amylomaltase(AM), which has a large binding crevice accommodating up to 15 glucose units and can not only cleave amylose, but also facilitate the formation of large glycan rings [C. Roth et al, Sci. Adv. (2017)]. Trying to understand the mechanisms underlying these processes, our goal is to quantify the local glycan binding strength at each binding site of AM.

In order to be able to distinguish small scale interactions, we use an amylose trimer as a molecular probe, therefore still retaining the proper chemical environment for the central glucose unit. The simulations are carried out using an improved version of the glycam force field [Sauter, J., Grafmüller, A., J. Chem. Theory Comput. (2016)] which can better capture carbohydrate properties. Since conventional MD is prone to trapping in potential energy minima, we are using a novel kind of Hamiltonian Replica Exchange: repulsive-scaling REMD, where the Lennard-Jones amplitudes and radii are being scaled [Siebenmorgen, T. et al, J. Comput. Chem. (2020)], resulting in a scaled-up repulsion between sugar and protein with increasing replica number. The simulations confirmed strongest binding in the binding site while also revealing a dominant binding position. Upon mutating different residues in the vicinity of this position, the relevance of aromatic residues in carbohydrate binding could be confirmed.

oral #568 **on-site**

The In Silico Assessment of DNA Lesions by Radiations

Presenting author: **Lorenzo Petrolli**

University of Trento, Department of Physics, Statistical and Biological Physics, Trento, Italy

Co-author/s: Manuel Micheloni, Francesco Tommasino, Emanuele Scifoni, Gianluca Lattanzi, Raffaello Potestio

The (structural, molecular) integrity of DNA is constantly threatened by a variety of toxic vectors, from both endogenous and exogenous sources. Amongst the plethora of diverse DNA lesions, double strand breaks (DSBs), i.e. the close rupture of the covalent DNA backbone on both strands, are deemed to be the most critical: indeed, DSBs are associated with a non-zero (albeit rare) likelihood to be mis-corrected by the cell defense framework, leading to severe cellular outcomes such as chromosomal aberrations and genomic instabilities.

Cell irradiation by accelerated ions is a well-acknowledged mean to deliver massive amounts of energy within localized sub-cellular volumes, thereby yielding clusters of critical DNA lesions and effective rates of cell annihilation. In this talk, I will outline the most effective in silico approaches depicting the cascade of events following cell irradiation, from both a radiation biology and a biophysical perspective. Namely, I will briefly describe Monte Carlo track structure techniques, characterizing the distribution of events of energy deposition about a radiation track and the subsequent emergence of critical DNA lesions. Thus, I will show our most significant results from applying classic Molecular Dynamics at different resolution scales to the dynamical and kinetic assessment of (double strand break) DNA lesions.

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oral #574 **on-site**

Lipid Bicelles in the Study of Biomembrane Characteristics

Presenting author: **Matthias Pöhnl**

Friedrich-Alexander-Universität, Department Biology, Computational Biology, Erlangen, Germany

Co-author/s: Rainer Böckmann

Simulations of lipid membranes typically make use of periodic boundary conditions to mimic macroscopically sized membranes and allow for comparison to experiments performed e.g. on planar lipid membranes or on unilamellar lipid vesicles. However, the lateral periodicity partly suppresses membrane fluctuations or membrane remodeling, processes that are of particular importance in the study of asymmetric membranes – i.e. membranes with integral or associated proteins and/or asymmetric lipid compositions.

Here, we devised a simple albeit powerful lipid bicelle model system that (i) displays similar structural, dynamical and mechanical properties compared to infinite periodic lipid membrane systems, and allows (ii) for the study of asymmetric lipid bilayer systems, and (iii) the unperturbed formation of local spontaneous curvature induced by lipids or proteins in molecular dynamics simulations. In addition, the system is characterized by largely unbiased thermal fluctuations as opposed to standard bilayer systems. Application of the bicelle system for an asymmetric lipid composition resembling the plasma membrane reveals that the cholesterol density for a tension-free plasma membrane with a vanishing spontaneous curvature is larger by 28% within the extracellular leaflet compared to the cytosolic leaflet. The method is additionally applied to resolve a long-standing dispute on the effect of cholesterol on membrane characteristics.

oral #575 **on-site**

Exploring and Leveraging the Interplay Between System Properties and Model Resolution

Presenting author: **Thomas Tarenzi**

University of Trento, Department of Physics, Statistical and Biological Physics, Trento, Italy

Co-author/s: Thomas Tarenzi, Raffaello Potestio

Atomistic molecular dynamics (MD) simulations of biomolecular systems, boosted by the increasing computer power available and the improved accuracy of force fields, allow researchers to investigate processes at larger length and time scales within reasonable simulation times. The necessity to simulate a large number of particle is sometimes dictated by the biomolecule itself: our atomistic simulations of a therapeutic antibody in solution showed how the interplay between the protein domains makes it necessary to simulate the full antibody structure with respect to the sole antigen-binding domain, contrary to what is traditionally done [1]. However, many biological processes of interest are still out of reach even for state-of-the-art hardware, thus requiring the usage of simplified, coarse-grained representations of a molecule at a level of resolution that is lower than the atomistic one. In this spirit, for example, we applied coarse-grained MD simulations to study the spontaneous binding of bacterial toxins to membranes at different compositions, showing how the lipid polar head exposure stabilizes the anchoring that initializes the toxic activity [2]. However, such simplified models prevent the study of phenomena taking place at an atomistic scale; for this reason, we recently proposed a novel multi-resolution scheme, dubbed coarse-grained anisotropic network model for variable resolution simulations, or CANVAS, which allows one to employ and smoothly couple within the same setup the atomistic resolution with a varying degree of coarse-graining [3]. Here, we showcase the application of this modeling approach, and discuss how the most appropriate levels of resolution, along with the distribution of the retained interaction sites within the molecular structure, can be identified in a rigorous manner by making use of measures from information theory.

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[3] Fiorentini, R., Tarenzi, T. and Potestio, R., 2023. J. Chem. Inf. Model. DOI: 10.1021/acs.jcim.2c01311

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oral #123 **online**

Microscopic Understanding of Fatty Acid Binding with α-Lactalbumin at Molten Globule State

Presenting author: **Abhik Ghosh Moulick**

S N Bose National Centre For Basic Sciences, Department of Physics of Complex Systems, Soft Matter & Biophysics Group, Kolkata, India

Co-author/s: Jaydeb Chakrabarti

A molten globule (MG) state is an intermediate state of protein observed during the unfolding of the native structure. In MG states milk protein α-Lactalbumin (aLA) binds with oleic acid (OLA). This MG-aLA-OLA complex, popularly known as XAMLET performs cytotoxic activities against cancer cell lines. Earlier study shows that the MG state of protein behaves as an IDP where the disorder is induced by external denaturing conditions like low pH. It is known that the inherently dynamic nature of IDPs plays a key role in rapid ligand recognition. However, the microscopic understanding of ligand recognition ability in MG state of protein is not yet explored. Motivated by this, we explore binding of bovine aLA with OLA using all atom molecular dynamics(MD) simulations. We find the binding mode between MG-aLA and OLA using the conformational thermodynamics method. We also estimate the binding free energy using the umbrella sampling (US) method for both MG state and neutral state. We find that the binding free energy obtained from US is comparable with earlier experimental results. The steered molecular dynamics and machine learning techniques suggest that some of the binding sites act as essential coordinate (EC) in determining the fluctuations. The microscopic understanding of protein-ligand binding gives an in-depth understanding of facilitating the discovery, design, and development of drugs.

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2. P. A. Jennings and P. E. Wright, Formation of a molten globule intermediate early in the kinetic folding pathway of apomyoglobin, Science, vol. 262, no. 5135, pp. 892–896, 1993.

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6. A. G. Moulick, J. Chakrabarti, Microscopic understanding of fatty acid binding with α-lactalbumin at molten globule state (Manuscript under preparation).

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Section 2:

Poster List, sorted by Number

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#	**Last Name,** First Name	**Poster Title**	**On-site**	**online**
129	**Badillo**, Joel A.	Potential of Mean Force for the Acetylation of Glucose in Choline-Chloride Ethylene Glycol Deep Eutectic Solvent from QM/MM MD Simulations		**X**
133	**Padmanaban**, Rajashree	Interaction of Hydroxyapatite and TLR-4 Using In Vitro and In Silico Approaches		**X**
142	**Kolář**, Michal H.	Gating of the Ribosome Exit Tunnel by Constriction-Site Proteins	**X**	**X**
158	**Cofas-Vargas**, Luis Fernando	Molecular Basis for FOF1-ATP Synthase Allosteric Drug Development: Aurovertin Binding Site		**X**
159	**Munguía Salazar**, Paloma	F1 sector of the F1Fo-ATP Synthase of Staphylococcus Aureus: Conformational Characterization and Inhibitor Development		**X**
163	**Velarde**, Marco Vinicio	Comparison of Different Force Fields in the Determination of the Excess Chemical Potential of Thiophene in the [C4MIM] [BF4, Cl, Br, CH3COO] ILs		**X**
183	**V. Guzman**, Horacio	Quantitative Electrostatic Force Tomography for Proteinaceous Capsids in Interaction with an Approaching Nanoscale Substrate	**X**	
195	**Scherer**, Katharina	Effect of Transmembrane Domains on the Free Energy of Stalk Formation during Membrane Fusion	**X**	**X**
200	**Matthes**, Dirk	Interactions of Anle138b with α-Synuclein Fibrils in the Presence of Phospholipids	**X**	**X**
202	**Aldakul**, Yessenbek	Investigation of Non-Canonical Voltage-Sensing Mechanism in K2P Channels Using Molecular Dynamics Simulations	**X**	**X**
207	**Szöllösi**, Daniel	Investigation of the Altered Folding Kinetics of the N-terminal Transactivation Domain of p53 due to the Mutation P27A	**X**	**X**
218	**Riedmiller**, Kai	Predicting Reaction Barriers of Hydrogen Atom Transfer in Proteins	**X**	**X**

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#	**Last Name,** First Name	**Poster Title**	**On-site**	**online**
221	**Acharya**, Abhishek	L3 Loop Mediated Translocation of Charged Molecules Through the OmpF Channel	**X**	**X**
232	**Kambaine**, Naserian	Conformations and Stability of Capsaicin in Bulk Solvent: A Molecular Dynamic (MD) Simulation Study		**X**
236	**Jung**, Hendrik	"asyncmd" - A Python Library for Parallel Setup, Control and Analysis of Molecular Dynamics Simulations	**X**	**X**
239	**Ping**, Xiaofei	Coarse-Grained Simulation Model of TDP43 Liquid-liquid Phase Separation Behavior	**X**	**X**
240	**Das**, Chandan K.	Computer Simulations of Porphyrin-Based Nanomachines	**X**	**X**
245	**Palacio-Rodriguez**, Karen	Estimation of Kinetic Rates and Collective Variable Quality From Time-Dependent Biased Simulations	**X**	**X**
247	**Qian**, Xuliang	Molecular Mechanisms of a Novel Insect Cuticle Peptide-Based Nano-Capsule Platform		**X**
248	**Mukherjee**, Saumyak	Molecular Thermodynamics of Protein Condensate Formation from All-Atom MD Simulations	**X**	**X**
268	**Lytje**, Kristian	Combining MD and SAXS in Rigid-Body Optimizations	**X**	**X**
272	**Fatafta**, Hebah	The Effects of Lipid Binding, Neuronal Membrane, Oxidative Stress and Molecular Crowding on Amyloid Aggregation	**X**	**X**
275	**Martínez-León**, Alejandro	Overcoming Hysteresis in Ligand Binding Potential of Mean Force Calculations	**X**	**X**
283	**Sohraby**, Farzin	Characterization of Ligand Unbinding Mechanisms and Kinetics for NiFe Hydrogenase Mutants Using τRAMD	**X**	**X**
296	**Monego**, Debora *	Size-dependent Sedimentation of Nanocrystals: The Role of the Ligand Shell Structure		**X**

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#	**Last Name,** First Name	**Poster Title**	**On-site**	**online**
298	**Claveras Cabezudo**, Ainara	Scaling Protein-Water Interactions in the Martini 3 Coarse-Grained Force Field to Simulate Transmembrane Helix Dimers in Different Lipid Environments	**X**	**X**
299	**Schäfer**, Stefan	Atomistic Molecular Dynamics Simulations of Gasdermin Pores	**X**	**X**
300	**Maihöfer**, Michael	Bayesian Methods for Fluctuation X-Ray Scattering	**X**	**X**
303	**Chatzimagas**, Leonie	Simulation of Liquid Jet Explosions and Shock Waves Induced by X-Ray Free-Electron Lasers	**X**	**X**
306	**Sritharan**, Sujith	Molecular Modeling of Plasmodesm Organization by MCTP Proteins	**X**	**X**
314	**Schultze**, Steffen	Bayesian Structure Determination of Multiple Conformational Structures from Single-Molecule X-ray Scattering Images	**X**	**X**
316	**Briand**, Eliane	Constant pH Molecular Dynamics in GROMACS using λ-dynamics and the Fast Multipole Method	**X**	**X**
318	**Leidner**, Florian	Regulation of the Fungal Fatty Acid Synthase Through Conformational Selection	**X**	**X**
329	**Schäffner**, Malte	Conditions for the Occurrence of Michaelis-Menten Kinetics in Markov Models	**X**	
331	**Hui**, Chenggong	Potassium Channel Force Field Development Using ab Initio MD	**X**	**X**
332	**Kalutskii**, Maksim	Multiscale Mechanochemical Model of Microtubule Dynamics	**X**	**X**
333	**Boushehri**, Saber	Effect of O-Glycans on Structure and Friction of the Intrinsically Disordered Synovial Joint Protein Lubricin	**X**	
334	**Kozlowski**, Nicolai	Evaluation of the CHARMM36m Force Field Combined with the OPC Water Model for Protein Simulations	**X**	**X**

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#	**Last Name,** First Name	**Poster Title**	**On-site**	**online**
336	**Kasparyan**, Gari	Electroporation: Free Energy Landscape and Methods for Imposing Transmembrane-Potentials	**X**	**X**
337	**Rennekamp**, Benedikt	How Collagen is Designed to Tame its Radicals	**X**	**X**
344	**Chen**, Yixin *	A Minimal Markov Model for Rotary Catalysis of F1-ATPase		**X**
368	**Brosz**, Matthias	Martini 3 Coarse-Grained Force Field for Collagen	**X**	**X**
381	**Schmidt**, Lisa	Active vs Inactive - Using Alchemical Free Energy Simulations to Probe Stabilizational Effects within the Human Dopamine 2 Receptor	**X**	**X**
391	**Lam**, Chun Kei	Ion Conduction Mechanisms in Potassium Channels Revealed by Permeation Cycles	**X**	**X**
394	**Forget**, Selene	Impact of Conformational Shifts on the Hairpin Ribozyme Reactivity	**X**	**X**
406	**Bodosa**, Jessica	Metadynamics Study of Benzyltrimethylammonium Binding Free Energy to Emre Protein		**X**
408	**Castillo Tarazona**, Marcia Yineth	Understanding the Interaction Between Gold Nanoparticles Functionalized with Amino Acid Derivatives and Proteins with Positively Charged Residues.		**X**
414	**Heinz**, Frederick	Structure and Dynamics of a Biomimetic Hydrogel: Coiled-Coil Monomers Self-Assemble into Chains	**X**	**X**
419	**Teuffel**, Jonathan	Effects of Conformational Transitions and Redox Protein Binding on the Catalytic Properties of Cytochrome P450s Revealed by Ligand Egress Patterns	**X**	**X**
421	**Chavarria Rivera**, Joel	Free Energies of Stalk Formation - Comparison between All Atomistic and Martini Simulations	**X**	**X**
432	**Versini**, Raphaëlle	Molecular Dynamics Based Prediction of Fzo1's Transmembrane Domains Structure	**X**	**X**

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437	**Schäfer**, Joana-Lysiane	Rare Event Simulation for Bioactive Peptides	**X**	**X**
442	**Shylendran**, Ardhra	Ion-Cluster Morphology and Impact on the Structure and Dynamics of Diglyme Based Sodium-Ion Battery Electrolyte - A Molecular Simulation Study		**X**
452	**Rauda-Ceja**, Jesus Antonio	Cavity Hydration in MUP-1 and Influence on Nonclassical Hydrophobic Effect		**X**
458	**Ali**, Ahmed	Allosteric Communication in Photoswitchable PDZ3 Domain	**X**	**X**
460	**Sorout**, Nidhi	Effects of Boron Nitride Nanoparticles and Selected Osmolytes on the Secondary Structure of Aβ-Peptide in Aqueous Medium: Prevention of β-Sheet Formation.	**X**	**X**
464	**Buhr**, Jannik	KIMMDY 2.0: A Kinetic Monte Carlo Reactive Molecular Dynamics Framework	**X**	**X**
465	**Gabrielli**, Sara	Conformational Dynamics of Elongation Factor G: Looking for Unresolved Intermediates in Ribosomal Translation	**X**	**X**
466	**de Maeyer**, Annke	Viral mRNA Secondary Structures Affect the Thermodynamics of Frameshifting	**X**	**X**
470	**Dorbath**, Emanuel	Hierarchical Dynamics as Result of Log-Periodic Oscillations in Proteins	**X**	**X**
473	**Heß**, Lisa-Marie	Base-Pair Free-energy Differences Estimated from Frameshifting Efficiencies for SARS Coronavirus	**X**	**X**
476	**Jones**, Jesse	Simulations of the Proton Exit Channel in Cytochrome c Oxidase	**X**	**X**
479	**Tusha**, Gers	Exploring the Reactivity of Supramolecular Helicates as Confining Catalysts	**X**	**X**
480	**De Vecchis**, Dario	The Functional Interplay of the ABC Transporter Pgp with its Lipid Substrates	**X**	**X**
488	**Shakibi**, Saber *	A One-Bead-Per-Saccharide (1BPS) Model for Multiscale Modelling of the Brain ECM		**X**

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491	**Kim**, Hyuntae (Henry)	Unexpected Challenges in Molecular Dynamics Simulations of Large Systems	**X**	**X**
492	**Nagy**, Gabor	Role of disordered regions beyond the binding motif of the Measles virus NTAIL	**X**	**X**
494	**Gaurav**, Kumar	Multiscale Simulations of Molecular Recoginition by Phase Separated Mut-16: A Scaffolding Protein of Mutator Foci	**X**	**X**
495	**de Vries**, Reinier	Gating Transitions in the MthK Potassium Channel	**X**	**X**
497	**Mendez Otalvaro**, Edward Francisco	Pharmacological Modulation of Trek1 Channel	**X**	**X**
503	**Farcas**, Alexandra	Computational Design Optimization of Nanoparticle Based Delivery Vectors for the CRISPR/Cas9 System		**X**
518	**Stuke**, Jan Felix Maximilian	SUMO in Dense Protein Solutions	**X**	**X**
523	**Torres Constante**, Karen Odalys	Characterizing the Transport Pathway of ABCG36 Substrates Using Metadynamics	**X**	**X**
524	**Pietrek**, Lisa Maria	Structural Ensembles of Disordered Proteins and RNA from Hierarchical Chain Growth	**X**	**X**
525	**Finn**, Lauren	Investigating Allostery of a Bacterial Toxin	**X**	**X**
527	**Zschau**, Richard	Mechanism of Beta-Hairpin Formation in Azochignolin	**X**	**X**
528	**Diez**, Georg	Comparing Correlation Measures to Study Protein Dynamics	**X**	**X**
534	**Hegedus**, Tamas	Modeling the Soluble and Membrane-Bound Conformations of Syntaxin 17 SNARE Proteins	**X**	**X**
535	**Scherlo**, Marvin	Structural Insights into Conformational Changes During Protein Aggregation and Refolding by Combining Theoretical and Experimental Infrared Spectroscopy of Amid Bands	**X**	**X**
538	**Gunes**, Sude	In Silico Identification of Potential Ligand Binding Sites of Galactokinase 1 (GALK1) to Treat Classic Galactosemia		**X**

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541	**Jäger**, Miriam	Finding Unbinding Pathways in the A1 and A2 Adenosine Receptor Combining Targeted MD and Leiden Clustering	**X**	**X**
543	**Leitmann**, Katharina *	Refining Active Sites of Proteins to Sub-Ångström Resolution by Combining Theoretical and Experimental Infrared Spectroscopy		**X**
545	**Reboul**, Etienne	In Silico Study of Protease Activated Receptor 1 (PAR1) and Thrombin Receptor Activator Peptide 6 (TRAP-6)	**X**	**X**
546	**Ezat**, Ahmed	Study of The Binding Site Dynamics, Druggability and Cryptic Pocket Formation in Different Human Coronaviruses' Main Protease (Mpro)		**X**
547	**Kopec**, Wojciech	Identification of Metastable States of a Large-Conductance Mechanosensitive Channel (MscL) Using Enhanced Sampling Methods		**X**
555	**Althoff**, Philipp	Tracking Water Molecules and Ions: Investigating Channelrhodopsin Gate Opening with Molecular Dynamics Simulations	**X**	**X**
556	**Post**, Matthias *	Path Separation of Dissipation-Corrected Targeted Molecular Dynamics Simulations of Protein-Ligand Unbinding		**X**
557	**Sartore**, Sofia	Importance of Feature Selection for Markov State Models: A Case Study on HP35	**X**	**X**
559	**Jana**, Kalyanashis	Demonstrating the Function of the Surface-Exposed Lipoprotein BtuG in Efficient B12 Transport in Association with the Outer-Membrane BtuB Protein	**X**	**X**
560	**Böckmann**, Rainer	mRNA Lipid Nanoparticle Phase Transition	**X**	**X**
573	**Jamal**, Sehrish	Computational Structure Modelling and Dynamics of Influenza Encoded Viroporin in Host Lipid Membrane System	**X**	**X**
576	**Kuntze**, Ricarda	Exploration of Ion Permeation in the Gramicidin A Channel Using a Charge Scaling MD Approach	**X**	**X**

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* For Abstract, see Section 1: List of Oral Contributions

Hybrid Workshop, April 28-29, 2023
"COMPUTER SIMULATION AND THEORY OF MACROMOLECULES"

#	**Last Name,** First Name	**Poster Title**	**On-site**	**online**
581	**Goeppert**, Simone	Peptide Binding in MHC Receptors	**X**	**X**
582	**Ramírez**, Marco	Conformational Selection in the CBD Domain of Cre Recombinase		**X**
583	**Kohnke**, Bartosz	GROMACS Meets FMM - The Path to Highly Scalable Constant pH Electrostatics	**X**	**X**
586	**Barbieri**, Mariano	Reinforcement and Competition Between RNAPolII-Enhancer-Promoter Contacts and Cohesin-CTCF Loop Extrusion	**X**	**X**
588	**Öztürk**, Mehmet Ali	ReverseDock: A Web Server to Dock a Single Ligand to Multiple Protein Targets		**X**
590	**Popov**, Cristian	Role of Receptor-Receptor Interaction as Checkpoint in Immune Signaling	**X**	**X**
591	**Sucerquia**, Daniel	How a Stretching Force Differently Destabilizes Chemical Bonds on a Protein Backbone	**X**	**X**
593	**Trollmann**, Marius F. W.	One Ring to Rule Them All: Lugdunin's Disruptive Effects	**X**	**X**
596	**Stelzl**, Lukas	From the Integrative Atomic Resolution Ensembles of Disordered Proteins to Simulations of Phase Separated Condensates	**X**	
606	**Atik**, Seref Berk	Computational Analysis of the Interaction of HIV-1 Capsid and Nanobody Complex Structure with a Potential for Diagnostic Applications		**X**
607	**Aponte-Santamaría,** Camilo	Energetics and Permeation of Small Molecules Used for 3D-Laser Printing Across Biological Lipid Bilayers	**X**	**X**
774	**Beierlein**, Frank	DNA-Repair Mechanisms: Molecular Simulations and Computational Alchemy		**X**
810	**Stachowicz-Kusnierz**, Anna	Molecular Dynamics Study of Interactions between Nanoplasics and Lipid Membranes		**X**

* For Abstract, see Section 1: List of Oral Contributions

Poster #129 **online**

Potential of Mean Force for the Acetylation of Glucose in Choline-Chloride Ethylene Glycol Deep Eutectic Solvent from QM/MM MD Simulations

Presenting author: **Joel A. Badillo**

Universidad Michoacana de San Nicolás de Hidalgo, Facultad de Ingeniería en Tecnología de la Madera, Morelia, Mexico

Co-author/s: Marco Gallo, Jorge Garza, Pablo López-Albarrán

Deep eutectic solvents (DES) are a promising class of solvents composed of a hydrogen bond donor (HBD) and a halide or quaternary ammonium salt such as choline chloride (ChCl) salt. The DES are considering green solvents due to their null or negligible vapor pressure, easy to synthetize, cheap, and non-toxic properties, [1] which allows them to be used as solvents or catalysts in a broad range of applications such the pre-treatment and transformation of the lignocellulosic biomass to obtain valuable derivative compounds. [2] [3] [4] Acetylation of lignocellulosic derivatives, such as wood, is an important route to preserve and increase the service-life of wood products, and thus allowing the preservation of the environment (sustainable development, circular economy). [5]

In this work, we evaluate the role of the choline chloride ethylene glycol (ChCl/Etg) DES as solvent for the acetylation reaction of D-glucose (base molecule in cellulose) through the O6 position with acetic anhydride. The conversion was modeled through a quantum mechanics / molecular mechanics (QM/MM) approach. The D-glucose and acetic anhydride molecules were selected as the QM region and the ChCl/Etg DES (solvent) as MM region. After identify the reaction coordinate (ξ), the potential of mean force (PMF) was obtained from QM/MM umbrella sampling (US) [6] simulations and the weighted histogram analysis method (WHAM). [7] The reaction was found to be spontaneous (-10.19 kcal/mol), with an activation energy barrier of 16.67 kcal/mol at 100 °C. Radial distribution functions (RDFs) suggest a synergetic effect from the solvent (cation, anion, and HBD), which assist the separation of the leaving group along the transformation. Also, the acetylation reaction was carried out in the choline chloride urea (ChCl/U) DES at same conditions. However, the activation barrier was estimated as 20.80 kcal/mol. The large activation barrier agrees with the results reported by Abbott et al. [4] who evaluated the acetylation of cellulose and monosaccharides in DES, and found a limited product yield in the ChCl/U DES.

We hope the present work provides insightful information on the emerging process of the chemical transformation of lignocellulosic materials by using new green solvents such as DES.

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2023-04-21

* For Abstract, see Section 1: List of Oral Contributions

Poster #133 **online**

Interaction of Hydroxyapatite and TLR-4 Using In Vitro and In Silico Approaches

Presenting author: **Rajashree Padmanaban**

University of Madras, Department of Crystallography & Biophysics, Immunodynamics & Interface Laboratory, Chennai, India

Co-author/s: Ashitha K.C, Gopinath

Injectable, self-healing and pH-responsive hydrogels are smart drug delivery systems for controlled and localized therapeutic release of drugs and has attained vitalizing healing effects in variety of diseases that includes wounds, cardio-vascular diseases, and tumours. The design and preparation of an injectable, self-healing and pH responsive hydrogel for tuneable controlled release of drug is highly desired. Here, we report a new paradigm using a natural polymer (guar gum) and sodium borohydride (NaBH 4) for the preparation of hydroxyapatite (HAP) containing smart hydrogels in a simple, fast and economical way. NaBH 4 performs as reducing agent and sodium metaborate (NaBO 2) (from NaBH 4) behaves as a cross linking agent between guar gum and molecular chains. Imiquimod (IMQ), a small TLR agonist 7 were encapsulated into the hydrogel in situ. The hydrogel showed a quick gelation process, injectability and self-healing property of hydrogel were investigated. In nitro gel degradation, gelation time, porosity and swelling rate, protein adsorption and in vitro bio degradation study and cytotoxic assessment by MTT assay and invitro IMQ release behaviour from hydrogels were analysed. pH responsive behaviour was verified by in vitro IMQ release hydrogels in PBS solutions with different pH values. Together, this pH responsive self-healing, novel-injectable hydrogels serve as a promising candidate as drug delivery vehicles with uncontrolled delivery capacity.

* For Abstract, see Section 1: List of Oral Contributions

Poster #142 **on-site & online**

Gating of the Ribosome Exit Tunnel by Constriction-Site Proteins

Presenting author: **Michal H. Kolář**

University of Chemistry and Technology, Department of Physical Chemistry, Biomolecular Dynamics, Prague, Czech Republic

Co-author/s: Tereza Svatoňová, Michaela Černeková

All proteins in living organisms are synthesized by ribosomes. The peptide bonds between amino acids are formed deep in the large ribosomal subunit. The catalytic site of the subunit is connected with the ribosome exterior by a tunnel, through which nascent proteins pass. In bacteria, the narrowest part of the tunnel is lined by two ribosomal proteins uL4 and uL22 and there has been some controversy about the role of the constriction in protein synthesis. We use atomistic computer simulations to a test a hypothesis that the conformational dynamics of uL4 and uL22 allows closing of the tunnel. We determine free-energy landscape of the constriction in the empty tunnel and the tunnel containing various nascent peptides. According to our model, the tunnel remains open but the constriction width can vary notably.

* For Abstract, see Section 1: List of Oral Contributions

Poster #158 **online**

Molecular Basis for FOF1-ATP Synthase Allosteric Drug Development: Aurovertin Binding Site

Presenting author: **Luis Fernando Cofas-Vargas**

National Autonomous University, Institute of Chemistry, Biomacromolecular Chemistry, Mexico City, Mexico

Co-author/s: Paola Mendoza-Espinosa, Enrique García-Hernández

FOF1-ATP synthase performs diverse key regulatory functions in the cell membrane in addition to its central role in the mitochondria as the primary producer of ATP. A growing number of human pathologies, including hypertension, atherosclerosis, cancer, and some neurodegenerative, autoimmune, and aging diseases, have been linked to its dysfunction. Furthermore, the inhibition of this enzyme jeopardizes the survival of several bacterial pathogens that pose a threat to public health. FOF1-ATP synthase has emerged as a novel drug target for treating human diseases and combating antibiotic resistance. The rotary mechanism that drives FOF1-ATP synthase catalysis is based on multiple intra- and intersubunit communication events that generate transient pockets that provide the opportunity to develop new types of enzyme inhibitors. Significantly, numerous natural exogenous inhibitors bind to a number of these pockets outside of the catalytic sites, which can be considered "validated" inhibitor allosteric sites. To pave the way for the structure-based development of new allosteric drugs targeting FOF1-ATP synthase, we characterized the binding sites of the fungal antibiotic aurovertin computationally. Significantly, numerous natural exogenous inhibitors bind to a number of these pockets outside of the catalytic sites, which can be considered "validated" inhibitor allosteric sites. To facilitate the structure-based development of new allosteric drugs targeting FOF1-ATP synthase, we computationally characterized the binding sites of the fungal antibiotic aurovertin. Using molecular dynamics simulations and end-point binding free energy calculations, novel aspects of the aurovertin binding sites were revealed in terms of intra- and intersubunit communications, conformational trends, hot spot binding residues, and solvent sites, which could be utilized as pharmacophoric guides in virtual screening campaigns.

* For Abstract, see Section 1: List of Oral Contributions

Poster #159 **online**

F1 sector of the F1Fo-ATP Synthase of Staphylococcus Aureus: Conformational Characterization and Inhibitor Development

Presenting author: **Paloma Munguía Salazar**

National Autonomous University, Institute of Chemistry, Biomacromolecules, Mexico City, Mexico

Co-author/s: Luis Fernando Cofas Vargas, Enrique García Hernández

In this work, we explore as pharmacological targets for the development of antibiotics, the regions of the F1 sector of the ATP synthase of S. aureus which are equivalents to binding sites for Aurovertin B in B. PS3. As the three-dimensional structure of this enzyme complex for S. aureus has not been resolved experimentally to date and considering the high conservation of bacterial ATP synthase throughout evolution, we used the known three-dimensional structures of two closely related species to develop models by molecular homology of the F1 sector, which were validated in silico. Then, the areas equivalents to binding sites for Aurovertin B were characterized under a physicochemical and phylogenetic context; we also evaluated these areas in different conformations of the S. aureus ATP synthase, which were obtained from free Molecular Dynamics in Explicit Solvent (examined by Principal Component Analysis). Subsequently, pharmacophoric points were determined through Molecular Dynamics Simulations in Organic Solvent/Water Mixtures, which served as a guide for the massive coupling of pharmacological-type chemical libraries. Moreover, as a first step for the experimental validation of the in silico results, we generated a plasmid for heterologous expression in bacterial systems of the F1 sector of the F1Fo-ATP synthase of S. aureus.

* For Abstract, see Section 1: List of Oral Contributions

Poster #163 **online**

Comparison of Different Force Fields in the Determination of the Excess Chemical Potential of Thiophene in the [C4MIM] [BF4, Cl, Br, CH3COO] ILs

Presenting author: **Marco Vinicio Velarde**

Universidad Autónoma del Estado de México, Facultad de Ciencias, Toluca, Mexico

Co-author/s: Marco Gallo, Jorge López-Lemus

Thiophene and various aromatic sulfur compounds are amongst the most difficult pollutants to remove from fuels [1] and are an important source of air pollution emanating from automotive vehicle emissions in the form of sulfur oxides. [2,3].

Classical atomistic force fields (FF) of Ionic liquids (IL) with fixed partial charges reproduced structural, solvation and transport proprieties in some cases in reasonable agreement with experimental values by scaling the atomic charges [4,5], however in condensed phases, properties such as hydrogen-bond length, coordination numbers, viscosities, diffusion coefficients, dielectric constant differ from their corresponding experimental values.

Recent efforts to improve these classical non-polarizable forcefields, included the addition of Polarization effects using Drude oscillators, in this direction, various researchers have developed polarizable FF for ILs [4,6,7] reproducing more accurately both thermodynamic and transport properties. Unfortunately, there exists very few molecular simulations involving the use of polarizable forcefields in the determination of the excess chemical potential of thiophene within ILs.

References:

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* For Abstract, see Section 1: List of Oral Contributions

Poster #183 **on-site**

Quantitative Electrostatic Force Tomography for Proteinaceous Capsids in Interaction with an Approaching Nanoscale Substrate

Presenting author: **Horacio V. Guzman**

Universidad Autonoma de Madrid, Department of Theoretical Biophysics, Computational Bio-Soft Matter Physics, Madrid, Spain

Co-author/s: Christopher Cooper, Ian Addison-Smith, Willy Menacho

Electrostatic interactions are crucial for the assembly, disassembly and stability of proteinaceous viral capsids. Moreover, at the molecular scale, elucidating the organization and structure of the capsid proteins in response to an approaching nanoprobe/substrate is a major challenge in biomacromolecular research. In this talk, I will present a generalized electrostatic model, based on the Poisson-Boltzmann equation, that quantifies the subnanometric electrostatic interactions between an AFM tip and a proteinaceous capsid from molecular simulations snapshots. This allows us to describe the contributions of specific amino acids and atoms to the interaction force. The validation results are shown in terms of total electrostatic forces with previous semi-empirical generalized models at available length scales (d> 1 nm). Then, the interaction of the Zika capsid with conical, flat (substrate) and spherical AFM tips is tackled in a tomography-type analysis to identify the most important residues and atoms, showing the localized nature of the interaction. This method can be employed for the interpretation of force microscopy experiments in fundamental virological characterizations and in diverse applications, like trapping proteins with tailor-made substrates. Finally, we will discuss the environment effects in terms of salt concentration to the protein-cage function and possible transcapsid electrostatic interactions with nucleic acids.

* For Abstract, see Section 1: List of Oral Contributions

Poster #195 **on-site & online**

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

Presenting author: **Katharina Scherer**

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

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. Further, this free energy decrease scales linearly with the concentration of TMDs in the membrane and strongly depends on the hydrophobic mismatch between the TMD and membrane core as well as on the lipid composition. We could explain the free energy decrease upon insertion of TMDs with an increased disorder in the lipid packing quantified by the order parameter. Additionally, we observed that kinked TMDs promote stalk formation more as compared to straight TMDs. This observation is compatible with the interpretation of experimental studies, which suggested that the flexibility of the TMDs is a key factor in facilitating membrane fusion, but our simulations indicate that the mechanism is likely due to the kinked structure than due to the flexibility per se.

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* For Abstract, see Section 1: List of Oral Contributions

Poster #200 **on-site & online**

Interactions of Anle138b with α-Synuclein Fibrils in the Presence of Phospholipids

Presenting author: **Dirk Matthes**

Max Planck Institute for Multidisciplinary Sciences, Theoretical and Computational Biophysics, Computational Biomolecular Dynamics, Göttingen, Germany

Co-author/s: Leif Antonschmidt; Rıza Dervişoğlu; Benedikt Frieg; Christian Dienemann;, Andrei Leonov; Evgeny Nimerovsky; Vrinda Sant; Sergey Ryazanov; Armin Giese; Gunnar F. Schröder; Stefan Becker; Bert de Groot; Christian Griesinger; Loren B. Andreas

Aggregation of amyloidogenic proteins is a characteristic of multiple neurodegenerative diseases. Atomic resolution of small molecule binding to such pathological protein aggregates is of interest for the development of therapeutics and diagnostics. Here we investigate the interaction between α-synuclein fibrils and anle138b, a clinical drug candidate for disease modifying therapy in neurodegeneration and a promising scaffold for positron emission tomography tracer design. We used nuclear magnetic resonance spectroscopy and the cryogenic electron microscopy structure of α-synuclein fibrils grown in the presence of lipids to locate anle138b within a cavity formed between two β-strands. We explored and quantified multiple binding modes of the compound in detail using molecular dynamics simulations. Our results reveal stable polar interactions between anle138b and backbone moieties inside the tubular cavity of the fibrils.

* For Abstract, see Section 1: List of Oral Contributions

Poster #202 **on-site & online**

Investigation of Non-Canonical Voltage-Sensing Mechanism in K2P Channels Using Molecular Dynamics Simulations

Presenting author: **Yessenbek Aldakul**

Leibniz Research Institute for Molecular Pharmacology, Chemical Biology, Structural Chemistry and Computational Biophysics, Berlin, Germany

Co-author/s: Han Sun

Two-pore domain potassium (K2P) channels are major regulators of cell excitability and they play an important role in a wide range of physiological functions. The K2P family consists of 15 member proteins that form channels either as homodimers or heterodimers. Although K2P channels have been the target for a variety of different experimental and computational studies, many open questions still remain regarding the ion permeation, gating, and pharmacological regulation. One of such questions is related to the voltage gating behavior in many K2P channels, where a non-canonical voltage-sensing mechanism within the selectivity filter (SF) was proposed, but structural evidence from experimental and computational investigations is still lacking. Here, we performed atomistic molecular dynamics (MD) simulations of a series of K2P channels including TREK-2, TWIK-1, as well as TREK-2/TWIK-1 heterodimeric channels under positive and negative transmembrane voltages. MthK channel with canonical K+ SF architecture was also simulated and considered as a reference. From the microsecond MD simulations, we observed two dynamic hotspots in the SF region for all these channels, which are concentrated at the S1 and S3 binding sites. Under positive voltage, the SF of the TREK-2 and TREK-2/TWIK-1 channels remain stable and the inner binding sites stay dehydrated. When negative transmembrane voltage is applied, the SF of the TREK-2 and TREK-2/TWIK-1 channels becomes considerably more dynamic, allowing water molecules to enter the SF and occupy the inner binding sites. In contrast, the SF of the reference MthK channel, remains stable and dehydrated under both positive and negative voltages. The other extreme is TWIK-1 channel, which is a unique K2P channel with low intrinsic activity and linear current-voltage characteristics. MD simulations suggested that the SF of TWIK-1 are highly dynamic under both positive and negative voltages, where water replaces ions so that the SF switches to an ion-depleted state. In conclusion, we propose that the conformational arrangement at S1 and S3 binding sites play a key role in the voltage-sensing process of TREK channels. Under negative voltages, the SF of TREK channels resembles the TWIK-1 channel that contains a hydrated SF with minimal K+ occupation.

* For Abstract, see Section 1: List of Oral Contributions

Poster #207 **on-site & online**

Investigation of the Altered Folding Kinetics of the N-terminal Transactivation Domain of p53 due to the Mutation P27A

Presenting author: **Daniel Szöllösi**

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

Co-author/s: Supriya Pratihar, Gábor Nagy, Sarah Rauscher, Reinhard Klement, Christian Griesinger and Helmut Grubmüller

The p53 protein is also called the 'guardian of the genome' due to its central role in genetic stability. It interacts with numerous other proteins, mainly via the disordered N-terminal transactivation domain (NTAD). It has been shown that a helix can fold in the free NTAD from residue T18 to L26. Furthermore, the same helix has been found in stable protein complexes e.g. with MDM2. This helix is terminated by P27, a residue conserved in all mammalian organisms. NMR relaxation dispersion experiments revealed that mutation of P27 to alanine increases the exchange timescale from ~4 µs to ~250 µs for residues in the helix. The same mutation also increases the binding affinity to MDM2 by 10-fold. In order to elucidate the structural reasons for such a drastic alteration, we did extensive molecular dynamics simulations totaling 0.6 ms for the WT and 1.8 ms for the P27A mutant. Identification of transient tertiary structures in both peptides confirmed that the mutant visits longer-lived folded states, however, timescales are shorter compared to the NMR experiment. We suggest the reason for the structural changes is due to the increased conformational space opened by the mutation.

* For Abstract, see Section 1: List of Oral Contributions

Poster #218 **on-site & online**

Predicting Reaction Barriers of Hydrogen Atom Transfer in Proteins

Presenting author: **Kai Riedmiller**

Heidelberg Institute for Theoretical Studies (HITS), Department of Chemistry, Molecular Biomechanics, Heidelberg, Germany

Co-author/s: Patrick Reiser, Elizaveta Bobkova, Ganna Gryn'ova, Pascal Friederich, Frauke Gräter

Hydrogen atom transfer (HAT) reactions are important reactions in many biological systems. As these reactions are hard to observe experimentally, it is of high interest to shed light on them using simulations. Here, we present a machine learning model for the prediction of activation energies of HAT reactions. As the inference speed is high, this model enables evaluations of many chemical situations in rapid succession. It is trained on energy barriers calculated using hybrid density functional theory. We built and evaluated the model in the context of HAT in Collagen, but the same workflow can also be applied to HAT reactions in other biological or synthetic polymers. The access to fast predictions of HAT energy barriers, when combined with molecular dynamics in a kinetic Monte-Carlo scheme, paves the way towards reactive simulations.

* For Abstract, see Section 1: List of Oral Contributions

Poster #221 **on-site & online**

L3 Loop Mediated Translocation of Charged Molecules Through the OmpF Channel

Presenting author: **Abhishek Acharya**

Constructor University, School of Science, Computational Biophysics, Bremen, Germany

Co-author/s: Ishan Ghai, Claudio Piselli, Kalyanashish Jana, Jigneshkumar D. Prajapati, Roland Benz, Mathias Winterhalter, Ulrich Kleinekathöfer

Antibiotic translocation into Gram-negative bacterial cells is largely mediated through the outer membrane porin channels. Large body of studies have previously uncovered the key factors that govern the permeation process and identified empirically the rules of permeation - the properties of an efficient permeator. The findings have highlighted the importance of an ionizable amine. The mechanism underlying this charge preference is however unclear. In this work, we provide a mechanistic rationale behind the preference for molecules with a positively-charge moiety. Within this model, the antibiotic induced L3 loop dynamics plays a critical role. In our simulations, we find that molecules with a positive charge, that is also "accessible" for interactions with the L3 loop, can strongly promote conformational changes in the loop. It is speculated that the ensuing large-scale motions in the loop must promote the permeation of the molecule.

* For Abstract, see Section 1: List of Oral Contributions

Poster #232 **online**

Conformations and Stability of Capsaicin in Bulk Solvent: A Molecular Dynamic (MD) Simulation Study

Presenting author: **Naserian Kambaine**

University of Dodoma, Department of Chemistry, Dodoma, Tanzania

Co-author/s: Daniel M. Shadrack, Said A.H. Vuai

Capsaicin is an alkaloid effective in pain management related to rheumatoid arthritis, osteoarthritis and many other pain-related diseases. However, its clinical applications are hampered by its poor solubility. Understanding its solution conformation at molecular level will help explore its full potential as a therapeutic agent. In this study, molecular dynamics (MD) simulations of capsaicin in polar and non-polar solvents viz; water, methanol (MeOH), dimethylsulfoxide (DMSO) and dichloromethane (DCM) were carried out to establish its stability and conformation. The structural orientation, conformation, stability and solubility of capsaicin are solvent dependent. Capsaicin is relatively more stable and soluble in DMSO than in DCM, MeOH and water.

* For Abstract, see Section 1: List of Oral Contributions

Poster #236 **on-site & online**

"asyncmd'' - A Python Library for Parallel Setup, Control and Analysis of Molecular Dynamics Simulations

Presenting author: **Hendrik Jung**

Max Planck Institute of Biophysics, Theoretical Biophysics, Frankfurt, Germany

Co-author/s: Gerhard Hummer

We present "asyncmd'', an opensource python library facilitating flexible, programmatic and parallel setup, control, and analysis of an arbitrary number of molecular dynamics (MD) simulations on high performance computing (HPC) resources. The library currently supports the SLURM queuing system and the gromacs MD engine, but can be easily extended to other queuing systems and MD engines. Notable features of our library include the propagation of MD until any or all user-supplied conditions are fulfilled on the trajectory, the parallelized application of user defined (python) functions on existing or generated trajectories (including the automatic caching of calculated values), and a dictionary-like interface to the MD parameters. Since all computationally costly operations are submitted via the queuing system, the process running "asyncmd'' has a low computational footprint and can be run on the login node to control complex and long running simulation setups with dynamic dependencies. "asyncmd'' is therefore an ideal building block to implement e.g. the string method with swarms of trajectories, highly parallelized transition path sampling, forward flux sampling, the weighted ensemble method, and many more. Additionally, the submission via the queuing system ensures that the available HPC resources are efficiently shared with other users independent of them using "asyncmd'' or not.

* For Abstract, see Section 1: List of Oral Contributions

Poster #239 **on-site & online**

Coarse-Grained Simulation Model of TDP43 Liquid-liquid Phase Separation Behavior

Presenting author: **Xiaofei Ping**

Johannes Gutenberg University, Max Planck Graduate Center mit der Johannes Gutenberg-Universität Mainz (MPGC) & Institute of Molecular Biology (IMB) & Germany Faculty of Biology & KOMET 1, Institute of Physics, Lukas Stelzl Group, Mainz, Germany

Co-author/s:

TDP-43 (TAR DNA-binding protein 43) is a protein that involves in the pathogenesis of several neurodegenerative diseases, including Amyotrophic lateral sclerosis (ALS) and Frontotemporal lobar degeneration (FTLD).The formation of protein aggregates in the brain and spinal cord of patients is underpinned by the phenomenon of liquid-liquid phase separation (LLPS) phenomenon. I will introduce a molecular dynamics simulation model, Martini3 Go-like model and introduce a method to improve the model to capture the LLPS behavior of TDP-43 as determined by experiments. The molecular dynamics simulations highlight parts of the protein which may be driving phase separation in health and disease.

* For Abstract, see Section 1: List of Oral Contributions

Poster #240 **on-site & online**

Computer Simulations of Porphyrin-Based Nanomachines

Presenting author: **Chandan K. Das**

Ruhr University, Theoretical Chemistry, Molecular Simulation, Bochum, Germany

Co-author/s: Lars Schäfer, Kimoon Kim

The dynamics of biomolecular machines that are modulated by various chemical or physical signals, can be mimicked by embedding and confining artificial molecular machines within a nanocage in which their functions can be specifically controlled by external stimuli. One such approach is the construction of a supramolecular rotor embedded inside a Zn-bound porphyrin-based cage by encapsulation of a tetrazine-based linear axle through metal-ligand coordination bonds. Our quantum chemical calculations complement NMR experiments and show that, without external stimuli, the linear axle shows nearly no motion. Strikingly, the addition of pyridine derivatives as a Zn-coordinating ligand induces the rotary movement of the linear axle inside the nanocage. All-atom molecular dynamics simulations reveal 90° jump-like rotary motion of the rotor occurring in a stochastic manner. The application of such porphyrin-based cages is further extended towards synthetic channels for the translocation of molecules across biological membranes. The MD simulations show that glucose molecules can selectively pass through the nanocage at much higher rates than sterically more bulky sucrose molecules. Interestingly, the glucose transportation rate is found to be controllable by changing the length of alkyl chains attached to the windows of the nanocage.

* For Abstract, see Section 1: List of Oral Contributions

Poster #245 **on-site & online**

Estimation of Kinetic Rates and Collective Variable Quality From Time-Dependent Biased Simulations

Presenting author: **Karen Palacio-Rodriguez**

Max Planck Institute of Biophysics, Theoretical Biophysics, Frankfurt, Germany

Co-author/s: Hadrien Vroylandt, Lukas S. Stelzl, Fabio Pietrucci, Gerhard Hummer, Pilar Cossio

The gap between the long timescales associated with interesting biomolecular interactions and the short timescales that are accessible by atomistic simulations poses a challenge for the in-silico prediction of kinetics rates. Molecular dynamics simulations with an adaptive time-dependent bias enable efficient exploration of the conformational space of molecular systems. In particular, metadynamics [1] enhances the sampling by adding a history-dependent bias potential that favors the exploration of high-free energy conformations. The added bias also disrupts the dynamics of the system. We recover the unbiased dynamics by developing a method based on Kramers' theory, the Kramers time-dependent rate (KTR) [2], that gives the correct statistical model for the barrier-crossing rate when a time-dependent bias is added to the system. At the present, one of the main limitations of the methods aiming to recover rates from biased simulations is that they rely on the use of ideal collective variables (CVs). Therefore, the major advantages of our method are that one can extract the unbiased rate and at the same time measure the goodness of the CV. The CV quality is quantified with a parameter ($\gamma \in [0,1]$) in terms of the direct contribution of the bias to accelerate the dynamics. For ideal CVs, i.e., where the added bias acts along the direction of the true transition and helps to lower the effective barrier, we expect $\gamma = 1$. By contrast, we expect $\gamma \sim 0$ for poorly chosen CVs. We benchmarked the method on a double-well potential with a good and a poor biasing direction and demonstrated that γ can measure quantitatively the quality of a CV. Then, we apply the method to a complex protein-ligand interaction (CDK2-03K) using non-optimal CVs. We reproduced the experimental unbinding rate up to an order of magnitude discrepancy, outperforming the widely used infrequent metadynamics method [3,4]. Overall, KTR allows to estimate rates from simulations much shorter than the timescale of the processes, while correcting for the effect of sub-optimal CVs in a simple post-processing procedure.

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* For Abstract, see Section 1: List of Oral Contributions

Poster #247 **online**

Molecular Mechanisms of a Novel Insect Cuticle Peptide-Based Nano-Capsule Platform

Presenting author: **Xuliang Qian**

Nanyang Technological University, School of Mechanical and Aerospace Engineering (MAE), Gao Research Group, Singapore

Co-author/s: Haopeng Li; Harini Mohanram; Tian Liu; Huajian Gao; Jing Yu

Nano-capsules can be used to transport a variety of substances into eukaryotic cells. Herein, we develop a novel insect cuticle peptide (ICP)-based nano-capsule platform with the potential for future drug delivery applications. Originated from insect cuticular proteins, the ICPs can form hollow nano-sized capsules in mixed solvents, via an unusual liquid-liquid phase separation (LLPS) process. However, the underlying molecular mechanisms of ICP nano-capsule formation remains unclear. By combining molecular dynamics simulations, free energy calculations and biochemical experiments, we present the first study to unravel the mechanics of ICP self-assembly and encapsulation. ICPs can be spontaneously driven to the interface of mixing solvents due to free energy differences, forming a soft, fluid-like membrane, followed by solidification through extensive beta-sheet formation. We also demonstrate the tunability of ICP nano-capsules by controlling peptide sequences. With this work, we aim to pinpoint the molecular mechanisms of ICP nano-capsule formation, which is the basis for important biomedical applications, such as drug delivery, cancer therapy and precision medicines.

* For Abstract, see Section 1: List of Oral Contributions

Poster #248 **on-site & online**

Molecular Thermodynamics of Protein Condensate Formation from All-Atom MD Simulations

Presenting author: **Saumyak Mukherjee**

Ruhr University, Theoretical Chemistry, Molecular Simulation, Bochum, Germany

Co-author/s: Lars Schäfer

Liquid liquid phase separation (LLPS) of proteins that give rise to membraneless organelles in the form of protein condensates have been widely recognized as a major driver for a multitude of intracellular processes. Associated with the process of LLPS is a thermodynamic tug-of-war among the water molecules that are released from the protein hydration layers into the bulk and those which are retained inside the protein droplets. Additionally, the intra- and inter-protein interactions play a vital role in condensate formation. Using atomistic molecular dynamics simulations on an intrinsically disordered protein domain (Low complexity domain of Fused in Sarcoma RNA binding protein) we dissect the multiple thermodynamic contributions to LLPS and assess their individual significance in the process. Our investigation reveals that water plays a part as important as that of the protein itself. These results promise a universal outlook towards the thermodynamics of association processes in biology with a focus on the role of water.

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Poster #268 **on-site & online**

Combining MD and SAXS in Rigid-Body Optimizations

Presenting author: **Kristian Lytje**

Aarhus University, Interdisciplinary Nanoscience Center, Aarhus, Denmark

Co-author/s: Jan Skov Pedersen, Jochen Hub

SAXS has proven to be a powerful complementary low-resolution tool for determination of structure of large biomolecular complexes. The analysis is greatly facilitated by availability of high-resolution structures from protein crystallography, cryo-EM, and solution NMR. When structures are available of the whole complex, rigid-body refinement with suitable physical restraints can be performed by fitting to the experimental SAXS data. A significant contribution to the scattering signal of the complex comes from the hydration shell. Typically this shell is only generated once before the optimization, and is then attached to the complex. Both its scattering density and the excluded volume of the complex are then included as free parameters in the fit. We have developed our own software with a focus on self-consistency and fast performance. For self-consistency the hydration shell is re-generated at each step of the optimization with our own efficient algorithm, which also utilizes partial histograms and multithreading for better performance. The use of a new approach, where scattering density and excluded volume parameters are determined through an initial MD simulation, and thus do not appear as free fitting parameters, will be described. An additional MD simulation can be performed afterwards to ensure the two parameters do not deviate significantly during the optimization.

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"COMPUTER SIMULATION AND THEORY OF MACROMOLECULES"

Poster #272 **on-site & online**

The Effects of Lipid Binding, Neuronal Membrane, Oxidative Stress and Molecular Crowding on Amyloid Aggregation

Presenting author: **Hebah Fatafta**

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

Co-author/s: Birgit Strodel

Aggregation of the amyloid beta (Aβ) peptide into structured amyloid fibrils is a hallmark of Alzheimer's disease. Recently, research on aggregation processes, as a potential source of neuronal toxicity, has received much attention. However, the mechanism of aggregation and the source of toxicity remain challenging research questions. Here, we performed microseconds all-atom molecular dynamics simulations to model the real environmental conditions in the study of Aβ, where amyloid formation is influenced by other biomolecular reactions. In particular, we focus on (i) the interplay between Aβ42 dimers and the neuronal membrane, which contains mixtures of several lipid species, mimicking the in vivo composition (1), (ii) the effect of free lipids in the aqueous phase as possible interaction partners of Aβ42 on the peptide structure and its interaction with a lipid membrane (2), (iii) the effect of oxidized glycine residues Gly25, Gly29 and Gly33 of Aβ42 on its conformation and interaction with a lipid membrane (3), (iv) the effect of macromolecular crowding on Aβ16-22 aggregation. Collectively, our results highlight the role of hydrophilic interactions in driving close peptide interaction with the lipid partner from the lipid membrane. We also conclude that Aβ hydrophobicity alone is not sufficient for its folding, but it can do so after binding to a hydrophobic interaction partner, either lipid molecules or via dimer formation. In the case of crowding we found that the oligomer formation is enhanced. These studies provide valuable insight into the Aβ peptide in its biological environment, which is useful in advancing knowledge about the peptide and its relationship to Alzheimer's disease.

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* For Abstract, see Section 1: List of Oral Contributions

Poster #275 **on-site & online**

Overcoming Hysteresis in Ligand Binding Potential of Mean Force Calculations

Presenting author: **Alejandro Martínez-León**

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

Co-author/s: Jochen S. Hub

Accurate estimations of ligand binding free energies and elucidation of the corresponded binding pathways are key challenges in computational drug design. Umbrella sampling (US) molecular dynamics simulations (US) are widely used to tackle these challenges; however, they frequently suffer from massive hysteresis between the ligand binding and unbinding pathways, limiting the applicability of US for ligand-protein interactions. The convergence of US is affected by the complexity of the system, the selection of reaction coordinate(s), simulation time, and by the selection of additional restraints.

Here we test several flavors of US in the pentameric formate-nitrite-transporter from Plasmodium-falciparum (PfFNT), which has been identified as the Malaria lactate transporter and as a novel drug target[1], and which exhibits a deeply buried ligand binding site. We analyzed systematically the effects of restraints on protein and ligand as well as the use of sampling and relaxation techniques such as simulated annealing and simulated tempering. In combination, we identified an easy -to-use protocol for obtaining potentials of mean force (PMFs) of ligand binding with virtually negligible hysteresis, all based on trivially parallelizing US simulations. The protocols have been implemented into a highly automated Python module, rendering the setup transferable to similar systems (https://gitlab.com/md_tools/mdynamic).

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Poster #283 **on-site & online**

Characterization of Ligand Unbinding Mechanisms and Kinetics for NiFe Hydrogenase Mutants Using τRAMD

Presenting author: **Farzin Sohraby**

Technical University Berlin, Department of Chemistry, Theoretical Structural Biology, Berlin, Germany

Co-author/s:

The hydrogenase family of enzymes attracted attention recently due to their ability to act as efficient catalysts to oxidize hydrogen and produce biofuel ($H_2 \rightleftharpoons 2\,H^+ + 2\,e^-$). However, some of the members of this family of enzymes, namely FeFe and NiFe hydrogenases, are inhibited by gas molecules present in the environment, such as O_2 and CO. One possible strategy to achieve tolerant enzymes can be blocking the access of these inhibitors to the catalytic site by designing mutant forms. We focused on NiFe hydrogenase from Desulfovibrio fructosivorans and 10 different mutants, and utilized an enhanced sampling method called τRAMD (τ-Random Accelerated Molecular Dynamics) to simulate the unbinding events of the substrate (H_2) and inhibitors (O_2 and CO) in order to understand the mechanism of diffusion of these gas molecules through the 30 Å long tunnels of this enzyme. In τRAMD a force of constant magnitude and random orientation is applied to the center of mass of the ligand molecule, increasing the chances of observation of unbinding events, which usually happen beyond the timescale of conventional molecular dynamics simulations. For the mutants simulated so far, we found that results obtained using a force magnitude of 1 kcal/molÅ reproduce the ranking of kinetic rates observed experimentally for different mutants. For the future, we will simulate the unbinding events of all mutants in complex with the gas molecules and compare their metastable states and unbinding pathways to understand the factors modulating binding kinetics. Understanding the effect of these mutations on the unbinding events can help us to design new mutants to achieve O_2- or CO-tolerant NiFe hydrogenases.

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Poster #298 **on-site & online**

Scaling Protein-Water Interactions in the Martini 3 Coarse-Grained Force Field to Simulate Transmembrane Helix Dimers in Different Lipid Environments

Presenting author: **Ainara Claveras Cabezudo**

Max Planck Institute of Biophysics, Theoretical Biophysics, Frankfurt am Main, Germany

Co-author/s: Christina Athanasiou, Alexandros Tsengenes, Rebecca Wade

Martini 3, the latest version of the widely used Martini force field for coarse-grained molecular dynamics simulations, is a promising tool to investigate proteins in phospholipid bilayers. However, simulating other lipid environments, such as detergent micelles, presents challenges due to the absence of validated parameters for their constituent molecules. Here, we propose parameters for the micelle-forming surfactant, dodecylphosphocholine (DPC). These result in micelle assembly with aggregation numbers in agreement with experimental values. However, we identified a lack of hydrophobic interactions between transmembrane helix protein dimers and the tails of DPC molecules, preventing insertion and stabilization of the protein in the micelles. This problem was also observed for protein insertion by self-assembling 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) or dipalmitoylphosphatidylcholine (DPPC) bilayers. We propose the reduction of the non-bonded interactions between protein and water beads by 10% as a simple and effective solution to this problem that enables protein encapsulation in phospholipid micelles and bilayers without altering protein dimerization or bilayer structure.

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Poster #299 **on-site & online**

Atomistic Molecular Dynamics Simulations of Gasdermin Pores

Presenting author: **Stefan Schäfer**

Max Planck Institute of Biophysics, Theoretical Biophysics, Frankfurt am Main, Germany

Co-author/s: Gerhard Hummer

After their activation, gasdermins bind to the plasma membrane, oligomerize and spontaneously insert β-pores into the membrane that cause the cell to go into pyroptosis — a recently discovered inflammatory type of regulated cell death. The fully assembled gasdermin β-pores comprise around 30 subunits and measure approximately 20 nm in diameter. The exact order and mechanism by which binding, oligomerization and formation of these large pores occur, however, remain elusive.

We performed atomistic multi-microsecond molecular dynamics simulations of different-size gasdermin-D (GSDMD) oligomers in pore and pre-pore conformations to study their lipid interactions, dynamics and structural stability. Using a complex asymmetric plasma membrane mimetic, we were able to identify conformation specific interactions with acidic lipids that recruit GSDMD to the inner leaflet of the plasma membrane and may drive oligomerization as well as insertion of the β-sheet. In addition, we find that already small oligomers comprising 2-10 subunits remain stably membrane inserted and form small pores that allow for water and ion flow across the membrane. For larger oligomeric arcs we identified the high force exerted by an emerging membrane edge as the driving force behind the formation of the slit and ring shaped pores. We quantify the membrane edge tension of our plasma membrane mimetic at 86 pN.

Our simulations thus provide an explanation for the sublytic, nonselective ion flux observed in the early stages of pyroptotic cell death and the formation and stability of arc, slit and ring shaped pores as seen through atomic force microscopy (AFM). They further point towards competing, lipid-dependent assembly pathways by a gradual expansion of sublytic pores at low GSDMD concentrations and a concerted "cookie-cutter" membrane insertion from prepore rings at high concentrations.

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Poster #300 **on-site & online**

Bayesian Methods for Fluctuation X-Ray Scattering

Presenting author: **Michael Maihöfer**

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

Co-author/s: Helmut Grubmüller

Fluctuation X-ray scattering is an emerging method for biomolecular structure determination, where scattering data of an ensemble of molecules in a dilute solution is collected using ultra-short X-ray pulses below rotational tumbling times. This allows to capture structural information in angular intensity correlations that are absent in traditional solution X-ray scattering methods, while also keeping the more biological conditions in solution compared to single-molecule X-ray scattering. However, the reconstruction of the molecular structure of the sample using the scattering images poses a significant challenge, since the orientations of the individual molecules in the solution are unknown and the low signal-to-noise ratio has to be overcome.

We present a rigorous Bayesian framework that finds the molecular structure that has the largest probability given all recorded scattering images. In this approach, the orientation of each molecule explicitly appears in the likelihood function. We formally integrate out the unknown individual orientations, and to reduce the computational cost, this integration is approximated by a finite sum over randomly chosen orientations of each molecule.

We show that our method can recover the molecular structure of a fictitious 12-atom molecule up to 4Å resolution, using 2000 synthetic noise-free images of 50 randomly oriented copies each.

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Poster #303 **on-site & online**

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

Presenting author: **Leonie Chatzimagas**

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

Co-author/s: Jochen 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 #306 **on-site & online**

Molecular Modeling of Plasmodesm Organization by MCTP Proteins

Presenting author: **Sujith Sritharan**

University of Paris, Institut of Biology Physico-Chemistry, Laboratory of Theoretical Biochemistry, Paris, France

Co-author/s: Antoine Taly, Emmanuelle Bayer

In plants, intercellular communication is primarily achieved through plasmodesmata. These membrane pores cross the cell wall and create symplastic continuity between cells [1]. Plasmodesms are crucial in coordinating developmental processes and defence mechanisms against pathogens.[2] They are also hijacked by viruses that can structurally modify them to propagate their viral genome from cell to cell.

Plasmodesms have a unique membrane organization: they are crossed by a "tube" of endoplasmic reticulum (ER), which is in intimate contact with the plasma membrane (PM), delimiting the pores. The two membranes are only a few nm apart (~10 nm) and connected by "tethers". The multiple C2 domains and transmembrane region protein (MCTP) family, critical regulators of cell-to-cell signalling in plants, act as ER-PM tethers, specifically at plasmodesmata [2,3]. However, the molecular mechanism and function of membrane tethering within plasmodesmata remain unknown. Furthermore, MCTP proteins are still poorly known at the level of the 3D structure.

Thus, we first generated structural models of A. thaliana MCTP by different prediction methods using deep learning like AlphaFold and RosettaFold [4], [5]. Then, we compare them by computing the rsmd and contact maps. Further, the movement of transmembrane regions in the lipid bilayer was characterised by coarse-grained simulation using the MARTINI3 force field and principal components analysis. We were finally able to extract representative conformations from our simulations.

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* For Abstract, see Section 1: List of Oral Contributions

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* For Abstract, see Section 1: List of Oral Contributions

Poster #314 **on-site & online**

Bayesian Structure Determination of Multiple Conformational Structures from Single-Molecule X-ray Scattering Images

Presenting author: **Steffen Schultze**

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

Co-author/s: Helmut Grubmüller

Single molecule X-ray scattering experiments are a promising method for the structure determination of biomolecules. However, the refinement of structures from these experiments is challenging: The scattering images are sparse, each containing only 10-50 photons on average, the signal-to-noise-ratio is very low, and the molecule orientations at the time of scattering are unknown. In addition, many biomolecules show structural heterogeneity and conformational dynamics between different distinct structures; to extract these structures from single molecule scattering data has so far been elusive. The main bottleneck here is that not only the orientation, but also the current conformer for each scattering image is unknown. Using a rigorous Bayesian approach, we demonstrate that it is possible to determine not only a single structure, but an entire structural ensemble from these experiments. Using synthetic scattering images generated from molecular dynamics trajectories, we extracted ensembles of eight alanine dipeptide conformers at 2Å resolution using 10^6 images, and the unfolded ensemble of the protein chignolin at 5Å resolution using 10^8 images. Unexpectedly, much fewer images are required to determine multiple conformational structures than a single structure of the same total number of degrees of freedom.

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Poster #316 **on-site & online**

Constant pH Molecular Dynamics in GROMACS using λ-dynamics and the Fast Multipole Method

Presenting author: **Eliane Briand**

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

Co-author/s: Bartosz Kohnke, Carsten Kutzner, Helmut Grubmüller

The residue protonation state of biomolecules is usually treated as fixed in molecular dynamics (MD) simulations: this is equivalent to a time-varying pH. On the other hand, constant pH MD methods propose to dynamically alter protonation to simulate at a given pH. We present an implementation of one such method in Gromacs, using Fast Multipole Method electrostatics and building upon the established λ-dynamics method with Hamiltonian interpolation. Beyond charge and Coulomb interaction, the role of bonded parameters interpolation is discussed, as well as applications to proteins.

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Poster #318 **on-site & online**

Regulation of the Fungal Fatty Acid Synthase Through Conformational Selection

Presenting author: **Florian Leidner**

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

Co-author/s: Helmut Grubmüller

The fungal type 1 fatty acid synthase (FAS1) is a paradigm for multifunctional metabolic enzymes. The α6β6 heterododecamer is composed of six catalytic units, arranged in a barrel shaped hollow body. Each catalytic unit contains a copy of the six enzymatic domains required for de novo fatty acid synthesis and an integral acyl carrier protein (ACP), responsible for the transfer of reaction intermediates. It is assumed that stochastic diffusion of ACP drives fatty acid synthesis, whereas spatial organization of enzymatic domains facilitates productive encounter. In this model, the supramolecular structure of FAS1 acts as a rigid framework. However, it has recently been discovered that binding of a regulatory subunit causes substantial structural rearrangements of FAS1, concomitant with relocation of ACP. It is therefore conceivable that the catalytic activity is coupled to both the conformational dynamics of the FAS1 complex and the stochastic dynamics of the ACP. Here we use large-scale molecular dynamics simulations to contrast the conformational dynamics of the yeast FAS1 with and without regulatory subunit. We find that FAS1 can sample distinct conformations at the microsecond timescale. Binding of the regulatory regulatory subunit rigidifies the complex and attenuates the conformational dynamics. At the same time, the regulatory subunit stabilizes binding of ACP to the acetyltransferase domain. Overall, our results show, that the FAS1 is not a rigid framework, but cycles between distinct conformations. The conformational dynamics described here are akin the conformational cycling of the metazoan FAS1 that is correlated with distinct enzymatic activities. Further evidence is required to show if this correlation is also a general property of the fungal FAS1. However, binding of the regulatory subunit indeed suggests that subtle changes in conformational dynamics correlate with changes in enzymatic activity.

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Poster #329 **on-site**

Conditions for the Occurrence of Michaelis-Menten Kinetics in Markov Models

Presenting author: **Malte Schäffner**

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

Co-author/s: Helmut Grubmüller

In a recent approach Markov models are used to determine the order of conformational changes, binding and unbinding events that a protein cycles through to perform its function. Therefore, most likely or probable Markov models of the protein given a data set are determined via maximum likelihood estimation or Bayesian interference, respectively.

When applying this method to our model enzyme ABCE1, almost all Markov models have a concentration-dependent turnover rate that is either completely or has pieces identical to the Michaelis-Menten kinetics. The high occurrence of Michaelis-Menten kinetics was unexpected because the Markov models of ABCE1 with 13 states and six concentration-dependent rates are more complex than the Markov model with only two states and one concentration-dependent rate required to derive the Michaelis-Menten kinetics.

To address this discrepancy, we quantified the occurrence of Michaelis-Menten kinetics in sparsely connected Markov models with up to 1000 states and log-uniformly distributed transition rates as well as its dependence on the number of concentration-dependent rates. We observe that the occurrence of Michaelis-Menten kinetics, firstly, has a symmetry with respect to half of all transition rates being concentration dependent, secondly, depends on the absolute number of concentration-dependent transition rates irrespective of the number of states, and thirdly, is correlated with the parameters of the log-uniform distribution. To qualitatively explain our observations, we derived conditions for the occurrence of Michaelis-Menten kinetics based on the analytical expression for the steady state population of a Markov model given by the matrix tree theorem, contributing further to the understanding of the ubiquity of the Michaelis-Menten kinetics.

* For Abstract, see Section 1: List of Oral Contributions

Poster #331 **on-site & online**

Potassium Channel Force Field Development Using ab Initio MD

Presenting author: **Chenggong Hui**

Max Planck Institute for Multidisciplinary Sciences, Theoretical and Computational Biophysics, Computational Biomolecular Dynamics, Göttingen, Germany

Co-author/s: Wojciech Kopec, Bert 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 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 permeations which leads to a low permeation rate.

* For Abstract, see Section 1: List of Oral Contributions

Poster #332 **on-site & online**

Multiscale Mechanochemical Model of Microtubule Dynamics

Presenting author: **Maksim Kalutskii**

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

Co-author/s: Helmut Grubmüller, Maxim Igaev

Microtubules are an essential component of the cell cytoskeleton. The network of microtubules plays a crucial role in regulating cell growth and movement, intracellular trafficking and mitosis. Microtubules, which assemble from αβ-tubulin heterodimers, are highly dynamic structures that alternate between steady growth and rapid shrinkage, fueled by the fundamental reaction of GTP hydrolysis. During this process, known as "dynamic instability", microtubules can generate pushing and pulling forces on other cellular compartments. However, we do not yet fully understand exactly how microtubules self-assembly and transmit mechanical force. Moreover, physical constraints present within the cell cause microtubule to bend and fracture, resulting in intricate collective phenomena such as softening and self-repair, which are still elusive.

Despite the importance of microtubules, their highly dynamic nature makes it hard to study their structure and dynamics experimentally. On the other hand, there are no multiscale computational approaches to predict the impact of subtle tubulin changes driven by GTP hydrolysis on the large-scale behavior of microtubules. Recent advances in exascale molecular dynamics (MD) simulations have enabled us to calculate microsecond fluctuations of microtubule end models; however, it is challenging to extrapolate this knowledge to real-life (>1 sec) timescales.

To overcome these limitations, we have developed a new coarse-grained model based on the discrete elastic rod representation and parameterized ab initio, using only all-atom molecular dynamics simulations and free energy calculations. The Hamiltonian function includes terms that describe both the bending-torsional elasticity of individual tubulin strands as well as the interactions between tubulin dimers. The model can be simulated using Brownian dynamics approaches with significantly larger time steps compared to classical MD, thus allowing us to reach biologically relevant time and size scales.

* For Abstract, see Section 1: List of Oral Contributions

Poster #333 **on-site & online**

Effect of O-Glycans on Structure and Friction of the Intrinsically Disordered Synovial Joint Protein Lubricin

Presenting author: **Saber Boushehri**

Karlsruhe Institute of Technology (KIT) / Heidelberg Institute for Theoretical Studies (HITS), Institute of Physical Chemistry, Theoretical Chemical Biology / MBM, Karlsruhe, Germany

Co-author/s: Camilo Aponte-Santamaría, Frauke Gräter

Lubricin is one of the main compounds responsible for providing excellent lubrication by reducing friction in synovial joints. Lubricin is a highly glycosylated protein, which contains an intrinsically disordered segment and a folded element. The role of glycans on the Lubricin conformation and, more generally, the molecular mechanisms by which Lubricin acts as a lubricant are yet to be fully understood.

Here, we used atomistic molecular dynamics simulations under equilibrium and shearing conditions (non-equilibrium) to elucidate the molecular mechanism behind the Lubricin low friction properties. For this purpose, we generated a set of intrinsically disordered fragments from the Lubricin sequence, which are representative of the main physicochemical properties of this protein, including glycosylation and proline content.

Our simulations demonstrate that the more glycosylation sites are added, the more negatively charged the fragments become, and thereby the more extended the Lubricin's intrinsically disordered fragments are. Accordingly, the size of the fragments appears to follow the same charge-dependency as other intrinsically disordered proteins. Non-equilibrium molecular dynamics simulations are allowing us to determine the effect of Lubricin, and more specifically its glycans, on the shear viscosity of the medium. Our results show how glycans impact locally the conformation of lubricin a result of relevance at understanding the molecular determinants underlying the low friction properties induced by this intrinsically disordered protein.

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Poster #334 **on-site & online**

Evaluation of the CHARMM36m Force Field Combined with the OPC Water Model for Protein Simulations

Presenting author: **Nicolai Kozlowski**

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

Co-author/s: Helmut Grubmüller

The accuracy of atomistic molecular dynamics (MD) simulations depends on the accuracy of the used force field. For proteins many force fields have been developed so far, each in combination with a particular water model. Typically, combining a protein force field with a water model for which is has not been developed is not expected to yield reliable results. However, recently the combination of the CHARMM36m force field with the OPC water model was shown to accurately estimate the compactness and secondary structure content of intrinsically disordered proteins. Whether CHARMM36m+OPC yields similar accuracy for globular proteins as well has, however, not yet been evaluated systematically. Here, we benchmark this combination on a set of six different globular proteins. To this end, we performed 50×1µs MD simulations per protein using CHARMM36m+OPC and, for comparison, the same simulations using the well-established Amber99SB-ILDN+TIP4P force field. We compared the generated ensembles by means of RMSD, radius of gyration and secondary structure content and also compared the conformational dynamics. We found that CHARMM36m+OPC generates less compact ensembles and shows higher barriers for conformational transitions. Furthermore, we compared ensembles of both force fields to experimental crystal structures, B-factors, and NMR chemical shifts. Here, we found that both force fields compare equally well to experimental data, with CHARMM36m+OPC ensembles agreeing with chemical shifts slightly better, whereas Amber99SB-ILDN+TIP4P ensembles better agree with crystal structures. Overall CHARMM36m+OPC and Amber99SB-ILDN+TIP4P yield similar accuracy for globular proteins. Combined with earlier results for disordered proteins, these findings suggest that CHARMM36m+OPC should provide competitive accuracy for a broad range of disordered and folded proteins as well.

* For Abstract, see Section 1: List of Oral Contributions

Poster #336 **on-site & online**

Electroporation: Free Energy Landscape and Methods for Imposing Transmembrane-Potentials

Presenting author: **Gari Kasparyan**

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

Co-author/s: Jochen S. Hub

The formation of pores over lipid membranes by the application of electric fields, termed membrane electroporation, is widely used in biotechnology and medicine to deliver drugs, vaccines, or genes into living cells. Continuum models for describing the free energy landscape of membrane electroporation have been proposed decades ago, but they have never been tested against spatially detailed atomistic models. Using molecular dynamics (MD) simulations with a recently proposed reaction coordinate, we computed potentials of mean force of pore nucleation and pore expansion in lipid membranes at various transmembrane potentials.

In MD the potentials can be implemented with external electric fields or by imposing charge imbalance between the two water compartments of a stacked double-membrane system. We show that, the two methods lead to (i) identical potentials of means force (PMFs) of pore formation and (ii) to identical polarization of water. However, using charge imbalance is technically more challenging. [1]

Whereas the free energies of pore expansion are compatible with existing continuum models, the experimentally important free energy barrier of pore nucleation is at variance with established models. We trace the discrepancy to incorrect assumptions on the geometry of the transition state; previous continuum models assumed the presence of a membrane-spanning defect throughout the process whereas, according to the MD simulations, the transition state of pore nucleation is typically passed before the defect encompass the whole thickness of the membrane. We developed a modified continuum model that qualitatively agrees with the MD simulations. [2]

[1] Gari Kasparyan, Jochen S. Hub; Equivalence of charge imbalance and external electric fields during free energy calculations of membrane electroporation; bioRxiv 2023.01.13.523896; doi: https://doi.org/10.1101/2023.01.13.523896

[2] Gari Kasparyan, Jochen S. Hub; Molecular simulations reveal the free energy landscape and transition state of membrane electroporation; bioRxiv 2023.01.31.526495; doi: https://doi.org/10.1101/2023.01.31.526495

* For Abstract, see Section 1: List of Oral Contributions

Poster #337 **on-site & online**

How Collagen is Designed to Tame its Radicals

Presenting author: **Benedikt Rennekamp**

Heidelberg Institute for Theoretical Studies (HITS), Molecular Biomechanics, Heidelberg, Germany

Co-author/s: Christoph Karfusehr, Frauke Gräter

Collagen is a force-bearing, hierarchical structural protein important to all connective tissue. In tendon collagen, high load even below macroscopic failure level creates mechanoradicals by homolytic bond scission, similar to polymers. The location and type of initial rupture sites critically decide on both the mechanical and chemical impact of these micro-ruptures on the tissue, but are yet to be explored.

We here use scale-bridging simulations to determine breakage points in collagen: In regular Molecular Dynamics (MD) simulations, covalent bonds are predefined and reactions cannot occur. To circumvent these limitations, we previously present our reactive Kinetic Monte Carlo / Molecular Dynamics (KIMMDY) scheme. Here, bond rupture rates are calculated based on the interatomic distances in the MD simulation and then serve as an input for a Kinetic Monte Carlo step. Recently, we have improved upon its accuracy with new Bond Dissociation parameters obtained by high-level quantum mechanical calculations. In additon, we have developed a much coarser model to bridge the gap to mesoscopic fibrils, allowing exploration of collagen's structural features in a computational accessible manner.

We find collagen crosslinks, as opposed to the backbone, to harbor the weakest bonds, with one particular bond in trivalent crosslinks as the most dominant rupture site. We identify this bond as sacrificial, rupturing prior to other bonds while maintaining the material's integrity. Also, collagen's weak bonds funnel ruptures such that the potentially harmful mechanoradicals are readily stabilized. Our results suggest this unique failure mode of collagen to be tailored towards combatting an early onset of macroscopic failure and material ageing.

* For Abstract, see Section 1: List of Oral Contributions

Poster #368 **on-site & online**

Martini 3 Coarse-Grained Force Field for Collagen

Presenting author: **Matthias Brosz**

Heidelberg Institute for Theoretical Studies (HITS), Institute for Scientific Computing, Molecular Biomechanics, Heidelberg, Germany

Co-author/s: Camilo Aponte-Santamaria, Frauke Gräter (in prep)

Collagen is the most abundant protein in the human body and the reason for the outstanding resilience and viscoelastic properties of the connective tissue. The collagen type I molecule is rich in glycine, hydroxyproline and proline amino acids and assembles into a triple helical structure, composed of three left-handed strands. On a larger scale, many of these 300 nm long collagen molecules form an intertwined microfibrillar structure exhibiting the 67-nm wide pattern of gap and overlap regions. At the transition between these regions, two triple helices are enzymatically crosslinked. Up to now, our atomistic models for the collagen fibril were limited to comprise only one gap and one overlap region (D-Band of 67 nm). With system sizes of around 2.5 million atoms, these were already on the upper side of what was previously computationally feasible. Therefore, we developed a coarse-grained model for collagen with the Martini 3 force field to enable computational studies of 300 nm long collagen microfibrils. We combined Boltzmann-inversion with a non-equidistant bond length potential to take the shape of the helical backbone into account, and performed non-equilibrium free energy calculations to select adequate beads types for each crosslink. Our Martini 3 model reproduces key structural and thermodynamic observables of single collagen helix, such as rise per residue, residues per turn, persistence length and stretching under force . With the Martini 3 collagen model at hand, we are now able to simulate microfibrillar collagen systems with different types (e.g. divalent or trivalent crosslinks) and also varying number of crosslinks to shed light on the propagation of forces through the fibril and in particular to analyze the influence on the overall stress-/strain behavior or D-band lengthening under mechanical load.

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Poster #381 **on-site & online**

Active vs Inactive - Using Alchemical Free Energy Simulations to Probe Stabilizational Effects within the Human Dopamine 2 Receptor

Presenting author: **Lisa Schmidt**

Max Planck Institute for Multidisciplinary Sciences, Theoretical and Computational Biophysics, Computational Biomolecular Dynamics, Göttingen, Germany

Co-author/s: Bert de Groot

G protein coupled receptors (GPCRs) are an important class of signal-transducing membrane proteins, able to bind various types of ligands and activate different cellular signalling pathways. Amongst the different types of GPCRs aminergic GPCRs are of particular interest as drug targets since they are important for neurological function and signal transduction in nerve cells. Out of those, we focus on the human dopamine receptor 2 (DRD2) and its activation mechanism.

We employ large mutational scans over the whole receptor domain and apply MD simulation based Alchemical Free Energy calculations with PMX to calculate free energy differences between active and inactive state. This will give us a better understanding of stabilizational effects within active and inactive state of this receptor. Our results will help to give deeper insights into DRD2s activation mechanism and help to create novel antipsychotic drugs.

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Poster #391 **on-site & online**

Ion Conduction Mechanisms in Potassium Channels Revealed by Permeation Cycles

Presenting author: **Chun Kei Lam**

Max Planck Institute for Multidisciplinary Sciences, Theoretical and Computational Biophysics, Computational Biomolecular Dynamics, Göttingen, Germany

Co-author/s: Bert de Groot

Potassium channels are responsible for the selective yet efficient permeation of potassium ions across cell membranes. Despite many available high-resolution structures of potassium channels, those conformations inform only on static information of the ion permeation processes. Here, we use molecular dynamics simulations and Markov state models to obtain dynamical details of ion permeation. The permeation cycles, expressed in terms of selectivity filter occupancy and representing ion permeation events, are illustrated. We show that the direct knock-on permeation represents the dominant permeation mechanism over a wide range of potassium concentration, temperature, and membrane voltage for the pore of MthK. Direct knock-on is also observed in other potassium channels with a highly conserved selectivity filter, demonstrating the robustness of the permeation mechanism. Lastly, we investigate the force field dependence of permeation cycles. Our results shed light on the underlying permeation details, which are valuable in studying conduction mechanisms in potassium channels.

* For Abstract, see Section 1: List of Oral Contributions

Poster #394 **on-site & online**

Impact of Conformational Shifts on the Hairpin Ribozyme Reactivity

Presenting author: **Selene Forget**

French National Centre for Scientific Research, Institut de Biologie Physico-Chimique, Laboratoire de Biochimie Théorique, Paris, France

Co-author/s: Marie Juillé, Élise Duboué-Dijon, Guillaume Stirnemann

The RNA world hypothesis poses a critical question regarding the emergence of autocatalytic networks in abiotic conditions. Ribozymes (RNA enzymes), which have been found to catalyze the reversible ligation of the phosphodiester bond - a key process for self-replication mechanisms-, appear as promising model systems for investigating prebiotic evolution.

In this study, our focus is on the small hairpin ribozyme, which stands out from other ribozymes due to its ability to favor ligation over cleavage without the need for ion assistance. Our aim is to provide a molecular understanding of the tertiary structure effect on the ligation/cleavage equilibrium using an all-atom molecular dynamics approach and to clarify the reaction thermodynamics and mechanism for this system.

We will present our first results regarding the identification of relevant conformations in the reactive state, which strongly depends on the force field parametrization and on the specific characteristics of the catalytic site in the initial structures. Specific emphasis was put on estimating the free energy landscape along several key variables, such as the inline attack angle of the cleavage reaction and the hydrogen bonds network. Beyond shedding light on the behavior of the hairpin ribozyme, our findings highlight the crucial importance of using specific enhanced sampling techniques to provide a reliable conformational sampling of the reactant and product states, which is typically not achieved even with microsecond brute force simulations.

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Poster #406 **online**

Metadynamics Study of Benzyltrimethylammonium Binding Free Energy to Emre Protein

Presenting author: **Jessica Bodosa**

University of Maryland, Biophysics, Laboratory of Molecular and Thermodynamic Modeling, College Park, United States

Co-author/s: Jeffrey Klauda

EmrE is a membrane protein found in bacteria such as E. coli that transports positively charged, aromatic toxins outside the cell. It is a parallel dimer and belongs to the small multidrug resistance (SMR) family. Although it is very small, 110 amino acids per monomer, its structure was not resolved at high resolution until recently. The toxin transport is associated with an alternating access movement of the protein monomers. The toxin binds to the protein while the two GLU14 residues of the EmrE are deprotonated in the high pH environment, and is released on the other side when a GLU14 is protonated in low pH. We use metadynamics to calculate the free energy of the binding path of benzyltrimethylammonium(BTMA) to EmrE in a model bacterial membrane. Two geometric reaction coordinates were chosen for the metadynamics runs, z-distance between ligand and the binding site, the angle of the ligand axis with the z-axis. Our results indicate that the free energy of bezyltrimethylammonium binding to EmrE is about -6.33kCal/mol. We also see interaction of the ligand with POPE and POPG lipids which may be involved in the binding-unbinding

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Poster #408 **online**

Understanding the Interaction Between Gold Nanoparticles Functionalized with Amino Acid Derivatives and Proteins with Positively Charged Residues.

Presenting author: **Marcia Yineth Castillo Tarazona**

Universidad de los Andes, Química, Computational Bio-Organic Chemistry, Bogota, Colombia

Co-author/s: Gian Pietro Miscione, Sebastián Franco Ulloa

Gold nanoparticles (AuNPs) functionalized with amino acid derivatives have generated great interest in biomedical applications. One of the main reasons for their application is their binding to proteins. Binding occurs through charge complementarity, meaning that negatively charged AuNPs bind to proteins that have ionized residues with a positive charge. Among these proteins are cytochrome C (Cit-C) and alpha-chymotrypsin (ChT). However, experimental reports have shown that the binding between negatively charged AuNPs with Cit-C and ChT is favored by different thermodynamic changes. Binding between AuNPs with Cit-C is favored by entropic changes, while binding between AuNPs with ChT is favored by enthalpic changes. Computational modeling methods such as molecular mechanics, molecular dynamics, and free energy binding calculations were used to explain the different thermodynamic behaviors. The changes in enthalpy and entropy in the binding of each AuNP-Protein complex found are due to displacement processes of water molecules on the surface of each protein, creation of hydrogen bonds at the AuNP-Protein interface, and maintenance of intermolecular hydrogen bonds between AuNP-solvent and/or protein-solvent. The difference in thermodynamic behaviors lies in the proportion of how these processes are distributed in each AuNP-Protein complex.

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Poster #414 **on-site & online**

Structure and Dynamics of a Biomimetic Hydrogel: Coiled-Coil Monomers Self-Assemble into Chains

Presenting author: **Frederick Heinz**

Free University of Berlin, Department of Biology, Chemistry, Pharmacy, Physical and Theoretical Chemistry, Berlin, Germany

Co-author/s: Jonas Proksch, Robert Schmidt, Bettina Keller

In this work we look into the biomimetic hydrogel hFF03 and try to understand its hydrogel nature. The most remarkable aspect of this poly peptide is, that is shows hydrogel properties in rheological studies at only 0.5 % polymer mass fraction. To understand how water retention under such properties is possible, we use molecular dynamics simulation to get a better understanding of its dynamics and nanoscale structure. For this we first generate model systems and verify them with experimental results. In a second step we simulate the self-assembly of fibre chains and analyze the changed behaviour for hFF03 with and without the chromophore amino benzoicacid.

* For Abstract, see Section 1: List of Oral Contributions

Poster #419 **on-site & online**

Effects of Conformational Transitions and Redox Protein Binding on the Catalytic Properties of Cytochrome P450s Revealed by Ligand Egress Patterns

Presenting author: **Jonathan Teuffel**

Heidelberg Institute for Theoretical Studies (HITS), Molecular and Cellular Modeling, , Heidelberg, Germany

Co-author/s: Goutam Mukherjee, Sungho Bosco Han and Rebecca C. Wade

Cytochrome P450 is a family of heme-containing monooxygenase enzymes, which play essential roles in drug-metabolism and steroid hormone biosynthesis. During their catalytic cycle, they undergo structural rearrangements and bind to electron transfer proteins such as cytochrome P450 reductase (CPR) or cytochrome b5. We found previously that interaction with CPR alters the egress-route distribution of CYP1A1, indicating a potential role of CPR in steering substrate uptake and enzymatic turnover. Here, we investigated the effects of 'open'/'closed' transitions of CYP2B4 and of redox protein binding to CYP17A1 on ligand egress route distributions, ligand residence times and the accessibility of the active site, by Random Acceleration Molecular Dynamics simulations of full-length, membrane-bound proteins.

All ligand residence times for CYP2B4 are shorter for the 'open' conformation and major egress routes from this conformation lead towards the membrane, indicating that substrate uptake/product release processes mainly occur in the 'open' conformation.

In contrast, the major egress route from CYP17A1 led towards the aqueous solvent. CPR binding opens membrane-bound routes whereas binding of CYb5 had a strong impact on egress of hydroxyprogesterone and hydroxypregnenolone. In the presence of CYb5, these compounds are further processed in a secondary lyase reaction, and the modulation of their egress may shed light upon the mechanism underlying this effect.

We found that the heme accessibility of the active sites of CYP17A1 and CYP2B4 changes during their catalytic cycles. Egress route patterns and residence times yield valuable information about the way in which cytochrome P450s are controlled to perform different functions at specific timepoints in their catalytic cycle.

* For Abstract, see Section 1: List of Oral Contributions

Poster #421 **on-site & online**

Free Energies of Stalk Formation - Comparison between All Atomistic and Martini Simulations

Presenting author: **Joel Chavarria Rivera**

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

Co-author/s: Katharina Scherer, Chetan Poojari & Jochen Hub

Stalk formation is one of the crucial steps in the membrane fusion pathway, as it leads to complete fusion of two opposing membranes. Understanding the molecular details driving stalk formation is important, since membrane fusion is one of the fundamental biological processes used during viral infection, reproduction, endocytosis, and exocytosis. Coarse-grained (CG) simulations have emerged as a powerful tool to study large-scale biological processes such as protein-lipid interactions, membrane fusion, due to their capability to simulate longer timescales with limited computational resources. Though the accuracy of CG simulations to reproduce experimental and atomistic protein-lipid interactions are well documented, it is yet to be established if CG simulations can also reproduce free-energies of stalk formation. In this study, we compute free-energies of stalk formation using CG Martini force field and atomistic force fields, to understand if CG force fields yield free-energies of stalk formation in agreement with all-atom force fields.

* For Abstract, see Section 1: List of Oral Contributions

Poster #432 **on-site & online**

Molecular Dynamics Based Prediction of Fzo1's Transmembrane Domains Structure

Presenting author: **Raphaëlle Versini**

Sorbonne University, CNRS, Departement Chimie Physique et Chimie Analytique, Laboratoire des Biomolécules (LBM), UMR 7203 ; Laboratoire de Biochimie Théorique (LBT), UPR 9080, Paris, France

Co-author/s: Marc Baaden, Antoine Taly, Patrick Fuchs

Outer mitochondrial membrane (OMM) fusion is an important process for the cell and organism survival, as its dysfonction is linked to neurodegenerative diseases and cancer. The OMM fusion is mediated by members of the dynamin-related protein (DRP) family, named mitofusins. Fzo1, the only mitofusin homologue of the yeast Saccharomyces cerevisiae and embedded in the OMM, was modeled in literature by homology with the mitofusin related bacterial dynamin-like protein (BDLP) as template. However BDLP does not possess any transmembrane part. Thus, the structure of the Fzo1 transmembrane domain, made of two putative helices TM1 and TM2, had to be determined using ab initio methods. One study in literature predicted the structure of Fzo1 transmembrane domain using the webserver PREDIMMER. Furthermore, TM1 has a lysine (Lys716) located inside the membrane which could either be protonated or unprotonated. The first construction assumed this lysine to be neutral.

Coarse-grained representations, with the force field MARTINI3, are used in order to sample a massive amount of conformations. We found that the neutral state of the LYS is preferable in the membrane. The most frequent contacts were also studied, and we found that the GX3G motif was often involved. A model was extracted and its robustness was tested using REMD simulations. The latter simulations allowed us to produce a refined version of the model.

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Poster #437 **on-site & online**

Rare Event Simulation for Bioactive Peptides

Presenting author: **Joana-Lysiane Schäfer**

Free University of Berlin, Institute for Chemistry and Biochemistry, Molecular Dynamics, Berlin, Germany

Co-author/s:

Bioactivity describes interactions that lead to effects on a living material can be described as rare events. A distinction can be made between slow internal dynamics and interactions between different molecules.

Cyclic cell-penetrating peptides (cCPPs) are an example of the latter, as they can cross membranes by a non-endosomal pathway and transport other molecules into a cell. There are cyclic peptides, such as cyclosporin A, where membrane permeability is due to an interplay between the conformational flexibility of the cyclic peptide and the amphiphilicity of its conformations.

One way to gain more insight into possible mechanisms for membrane transduction of various cCPPs is to analyze their structure and conformational dynamics. Computational methods, such as enhanced molecular dynamics sampling techniques and dynamic pathway reweighting for Markov state models can be used for this purpose.

* For Abstract, see Section 1: List of Oral Contributions

Poster #442 **online**

Ion-Cluster Morphology and Impact on the Structure and Dynamics of Diglyme Based Sodium-Ion Battery Electrolyte - A Molecular Simulation Study

Presenting author: **Ardhra Shylendran**

Indian Institute of Science Education and Research, Department of Chemistry and Center of Energy Sciences, Soft Matter Simulation Laboratory, Pune, India

Co-author/s: Prabhat. Prakash, Rabin. Siva Dev, and Arun Venkatnathan

Glyme-based sodium salt solutions exhibit excellent electrochemical properties as battery electrolytes since they could enable the co-intercalation of sodium into graphite [1,2]. For example, solutions of NaPF6 in glyme show exceptional chemical stability and better thermal stability than alternative carbonate-based electrolytes. The oxygen atoms present in the glyme molecules coordinate with the Na+ ion in an octahedral manner, which can also be referred to as solvated ionic liquids of the form [Na(glyme)]+---anion-, with an electrochemical window of 4 V and ionic conductivity of 1 mS/cm [3]. The understanding of the solvation behaviour of these electrolytes requires molecular-level exploration.

We perform computer simulations based on classical molecular dynamics and plane-wave density functional theory to mimic atomic interactions and ionic mobility.[4]. Unlike the previous experimental and theoretical works which usually explore only a 1 M concentration of liquid electrolytes, we have studied the structure and ion dynamics over a range of concentrations of NaPF6 in diglyme. The nature of the atomic interactions and the strength of these interactions were studied using radial distribution functions and uninterrupted lifetime analysis. The formation ion clusters were elucidated using the cluster analysis and dimer distribution function profiles suggesting that the Na+ ions mostly exist as solvated ions that are coordinating with solvent molecules (free ions or solvent-separated ion pairs). Also, some fraction exists as contact ion pairs, and very few as aggregated ion pairs those increasing slightly with temperature and more with ion concentration. The self-diffusion coefficients of Na+, PF6- ions, and the diglyme molecules were calculated using Einstein's relations from the mean-squared displacement of the respective species. The ionic mobility of Na+ and PF6- ions were modelled using both Nernst-Einstein's and correlated Nernst-Einstein's relations was validated with experiments.

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* For Abstract, see Section 1: List of Oral Contributions

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* For Abstract, see Section 1: List of Oral Contributions

Poster #452 **online**

Cavity Hydration in MUP-1 and Influence on Nonclassical Hydrophobic Effect

Presenting author: **Jesus Antonio Rauda-Ceja**

National Autonomous University, Institute of Chemistry, Laboratory of Biomacromolecules, Mexico City, Mexico

Co-author/s: Enrique García-Hernández; Luis Fernando Cofas-Vargas

Nonclassical hydrophobic effect is an enthalpy driven phenomenon that occurs in molecular recognition between hydrophobic ligands and sub-optimally hydrated concave hosts. To gain new insights into the molecular basis of this event, the Mus musculus major urinary protein-1 (mMUP-1) was characterized in silico and compared to the properties previously reported for bovine odorant binding protein (bOBP). Both proteins belong to the lipocalin superfamily, extracellular proteins involved in the transport of small hydrophobic molecules. It has been reported that ligand binding is driven by nonclassical hydrophobic effect in both mMUP-1 and bOBP, and the addition of methylene groups of congeneric series of ligands elicits a larger enthalpy decrease. 4-microseconds long molecular dynamic simulations of apoprotein mMUP-1 and complex with pentanol and nonanol revealed that mMUP-1 exhibits more protein-ligand contacts and a greater conformational landscape upon binding of longer ligands. In the apo state, the binding cavity possess two well-defined hydration sites and two mobile water molecules that tends to be released during complex formation. Nevertheless, ligand size does not appear to influence water molecule release, contrary to the bOBP behavior. The present work explores the heterogeneity of hydrophobic ligand molecular recognition through two lipocalins that display similar binding thermodynamic signature but different strategies.

* For Abstract, see Section 1: List of Oral Contributions

Poster #458 **on-site & online**

Allosteric Communication in Photoswitchable PDZ3 Domain

Presenting author: **Ahmed Ali**

University of Freiburg, Institute of Physics, Biomolecular Dynamics, Freiburg, Germany

Co-author/s: Steffen Wolf; Gerhard Stock

Allostery is one of the most important mechanisms for biomolecular regulation. Generally, it involves a perturbation such as a binding event at one side of a macromolecule to affect another distant functional site. However, how such a perturbation propagates through the protein in detail is still not well understood. To establish a minimal allosteric model system, the third PDZ domain (PDZ3) of the postsynaptic density-95 (PSD-95) protein has been considered. The PDZ3 domain binds to the C-terminus of target proteins and regulates the signal propagation in PSD-95. In addition to the common and conserved central β-sheets and two α-helices present in all PDZ variants, PDZ3 contains a third C-terminal α-helix (α3–helix) that packs against the β-sheet at a considerable distance to the ligand binding pocket.

In this work, we aim for a detailed understanding of the microscopic dynamics of allosteric communication between α3 and the ligand binding pocket. In addition, we explicitly aim at finding intraprotein changes appearing on the same time scales as found in recent time-resolved IR spectroscopic experiments. Consequently, we perform direct nonequilibrium molecular dynamics (MD) simulations of PDZ3, by attaching a photowswitch at the allosteric site (α3) and mimicking the initial cis → 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. We characterize the α3-switched response by correlation and timescales analysis, which reproduces experimental timescales accurately. Furthermore, we aim to construct Markov State Model (MSM) to describe the structural evolution of the allosteric process of PDZ3.

* For Abstract, see Section 1: List of Oral Contributions

Poster #460 **on-site & online**

Effects of Boron Nitride Nanoparticles and Selected Osmolytes on the Secondary Structure of Aβ-Peptide in Aqueous Medium: Prevention of β-Sheet Formation.

Presenting author: **Nidhi Sorout**

Saarland University, Center for Bioinformatics, Computational Biology, Saarbrücken, Germany

Co-author/s: Amalendu Chandra

The aggregation of amyloid β (Aβ) peptide triggered by its conformational changes leads to the commonly known neurodegenerative disease of Alzheimer's. The formation of β-sheets of the peptide plays a crucial role in its aggregation and subsequent fibrillization by acting as an amyloid seed. Here the primary aim of our study is to prevent the structural transition of Aβ-peptide into β-sheet conformation at initial stages. For that we have studied the various interaction between Aβ-peptide and boron nitride nanoparticles of different curvatures and some selected osmolytes. These external materials were found to inhibit β-sheet formation via different pathways so that it is trapped in an energy well of non-amyloid conformation and blocks and/or delays the fibril formation process.

* For Abstract, see Section 1: List of Oral Contributions

Poster #464 **on-site & online**

KIMMDY 2.0: A Kinetic Monte Carlo Reactive Molecular Dynamics Framework

Presenting author: **Jannik Buhr**

Heidelberg Institute for Theoretical Studies (HITS), IWR, Molecular Biomechanics, Heidelberg, Germany

Co-author/s: Eric Harmann, Benedikt Rennekamp, Kai Riedmiller

Forcefield based molecular dynamics simulations allowed us to reach biologically relevant timescales and system sizes. A fundamental limit of this molecular mechanics approach is a lack of reactivity. We present a framework for combining classical molecular dynamics simulations with a kinetic Monte Carlo approach to bridge timescales and allow reactions to occur within a simulation. It is implemented as a user-friendly, extensible python module based on the open-source high-performance molecular dynamics software suit GROMACS. This poster focusses on making the necessary changes to topologies and forcefield parameters in a modular way.

* For Abstract, see Section 1: List of Oral Contributions

Poster #465 **on-site & online**

Conformational Dynamics of Elongation Factor G: Looking for Unresolved Intermediates in Ribosomal Translation

Presenting author: **Sara Gabrielli**

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

Co-author/s: Helmut Grubmüller, Lars V. Bock

During protein synthesis, when the ribosome moves along the mRNA, the tRNAs bound to the ribosome translocate between different binding sites. Elongation Factor G (EF-G) is a GTPase that interacts with bacterial ribosomes and uses the energy from GTP hydrolysis to accelerate tRNA translocation. The final products of GTP hydrolysis are GDP and inorganic phosphate. Recent cryo-EM studies have shown that, after the release of the inorganic phosphate from EF-G's active site, a large overall reorientation of EF-G takes place in the ribosome. However, little is known about the intermediate conformations during this rearrangement. The high flexibility of domain IV observed in Cryo-EM studies and its proximity to the A-site tRNA suggest that the dynamics of domain IV might play a fundamental role during translocation. In order to investigate the conformational dynamics and energetics of EF-G, we use extensive all-atom Molecular Dynamics (MD) simulations. Simulations of E. Coli EF-G in solution have indeed revealed that the most pronounced inter-domain motion is the rotation of domains IV-V relative to domains I-III. The results have also provided an insight on the conformations that are intrinsically favored in the protein, i.e. independently from the interactions with the ribosomal environment. Starting from the observations here reported, we will integrate and compare the results of the simulations in solution with correlation-driven MD simulations of EF-G in the ribosome.

* For Abstract, see Section 1: List of Oral Contributions

Poster #466 **on-site & online**

Viral mRNA Secondary Structures Affect the Thermodynamics of Frameshifting

Presenting author: **Annke de Maeyer**

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

Co-author/s: Lisa-Marie Heß, Sara Gabrielli, Helmut Grubmüller, Lars V. Bock

During translation, the ribosome produces proteins by translating the sequence of nucleotides, contained in the mRNA, into a sequence of amino acids. Each triplet of nucleotides encodes one amino acid and the reading frame is set at the start of translation. A shift of the reading frame results in the synthesis of a different protein. Spontaneous frameshifting is rare, but many viruses have evolved programmed frameshifting sites with high probability of frameshifting thereby increasing the coding potential of their genome. For example, during -1 frameshifting, the ribosome "slips" on the mRNA, such that the reading frame is shifted by one nucleotide in comparison to the original 0 frame. Frameshifting occurs when translation is slowed down, giving the ribosome enough time to overcome the free-energy barrier between the 0 frame and the -1 frame. The slowdown of translation is often due to the presence of secondary structure elements in the mRNA (e.g. stem-loops or pseudoknots), which interact with the ribosome and impede its movement along the mRNA. Structural evidence has shown that stem-loop and pseudoknot interact differently with the ribosome during its movement along the mRNA. Thus, we hypothesize that the two mRNA structured elements differently affect the free-energy difference between the 0 and -1 frame. In order to test this hypothesis, we use a previously published free-energy model of frameshifting (Bock et al., 2019) and employ Bayesian statistics to estimate the free-energy differences between the 0 and the -1 frame from experimentally determined frameshifting efficiencies (Mikl et al., 2020). The results suggest that pseudoknots reduce the free-energy difference in contrast to stem loops, and therefore, enhance frameshifting efficiencies.

* For Abstract, see Section 1: List of Oral Contributions

Poster #470 **on-site & online**

Hierarchical Dynamics as Result of Log-Periodic Oscillations in Proteins

Presenting author: **Emanuel Dorbath**

University of Freiburg, Institute of Physics, Biomolecular Dynamics, Freiburg, Germany

Co-author/s: Steffen Wolf; Gerhard Stock

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 time scales in non-equilibrium simulations using logarithmic oscillations. At first, an 1-dimensional hierarchical system is used as proof of principle. As second system, the α-aminoisobutyric acid Aib9 is presented, which is a simple peptide whose hierarchical structure and relaxation times were studied in previous works. It has two stable conformations being a left- and right-handed helix. Finally, the PDZ2 domain in trans-to-cis transitions is studied as the most complex and challenging one of the three.

* For Abstract, see Section 1: List of Oral Contributions

Poster #473 **on-site & online**

Base-Pair Free-energy Differences Estimated from Frameshifting Efficiencies for SARS Coronavirus

Presenting author: **Lisa-Marie Heß**

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

Co-author/s: Annke de Maeyer, Sara Gabrielli, Helmut Grubmüller, Lars V. Bock

Every information needed for the synthesis of a protein is encoded in a specific sequence of mRNA nucleotides. Proteins are produced by the ribosome which reads three nucleotides at a time and translates each triplet into one amino acid with the help of tRNAs. Ribosomal translation typically follows the reading frame that is set when the ribosome reads the first triplet of nucleotides (0 frame). However, shifts of the reading frame may occur and lead to the synthesis of a different protein. Thus, frameshifting enables the storage of the information required for the synthesis of two different (poly-)proteins in one sequence. Frameshifting events rarely happen spontaneously, while programmed ribosomal frameshifting (PRF) has evolved in many viruses to increase the coding capacity of the genetic information. The most common type of frameshifting is -1 PRF, where the reading frame is shifted by one nucleotide "back" with respect to the 0 frame while two tRNAs are bound to the ribosome and form base pairs with the mRNA.

One of the factors determining the efficiency of frameshifting is the slippery sequence, where the shift in the reading frame happens. This sequence consists of seven mRNA nucleotides, which, after frameshifting, group into different triplets and, hence, form base-pairs with different tRNA nucleotides. According to a previously published thermodynamic model (Bock et al., 2019), the -1 frameshifting efficiency depends only on the free-energy differences of the base-pairs between the 0 and -1 frames.

While the thermodynamic model was previously applied on data obtained in vitro from E. Coli ribosomes, here we extend its application to high-throughput data obtained in an in-vivo environment from eukaryotic ribosomes (Mikl et al., 2020). In particular, we use Bayesian statistics to estimate base-pair free-energy differences from frameshifting efficiencies of SARS Coronavirus sequence variants.

* For Abstract, see Section 1: List of Oral Contributions

Poster #476 **on-site & online**

Simulations of the Proton Exit Channel in Cytochrome c Oxidase

Presenting author: **Jesse Jones**

Technical University Berlin, Institute for Biomolecular Modeling, Berlin, Germany

Co-author/s: M.A. Mroginski, V.R.I. Kaila, A.P. Gamiz-Hernandez

Cytochrome c Oxidase is the terminal enzyme of the cell respiratory chain, catalyzing the reaction of O2 to H2O. Proton pumping across the membrane occurs coupled to the reaction. This process converts energy into a membrane potential, contributing to the core energetic mechanism of the cell. The reaction at CcO (Cytochrome c Oxidase) is driven by the transfer of electrons from Cytochrome c to CcO, which then move through the enzyme and reduce O2 to H2O. To do this, the respective amount of protons needs to be transferred through the membrane too. While the larger part of the mechanism of the CcO reaction has been studied intensively, namely the uptake of protons as well as electron and proton transfer processes, the proton exit towards the P-side of the membrane has not been studied well to date. This study aims at providing key insight into the potential process of expulsion of a proton in the different redox-states and protonation states of the enzyme without observable channel openings and proton back flow. Key residues identified by [Gunner et al., 2018] are structurally and sequentially aligned to the residues in CcO of Par. Den. and pKa-values are calculated using the Karlsberg2+ lPBE-solving suite, providing a pKa-value driven pathway for the proton to exit.

* For Abstract, see Section 1: List of Oral Contributions

Poster #479 **on-site & online**

Exploring the Reactivity of Supramolecular Helicates as Confining Catalysts

Presenting author: **Gers Tusha**

Ruhr University, Theoretical Chemistry, Molecular Simulation, Bochum, Germany

Co-author/s: Lars Schäfer, Van Craen

Self-assembled metal-organic supramolecular complexes are emerging as promising biomimetic catalysts, giving rise to a different reactivity with respect to the widely explored chemistry in bulk solvents.

In this work, we investigate different supramolecular Zn-metallated helicates as catalysts toward an SN1-type nucleophilic substitution.

Relying on a synergistic interplay between classical Molecular Dynamics simulations on the one hand and semi-empirical quantum chemistry methods and Density Functional Theory (DFT) on the other, we explore the conformational space as well as the chemical reactivity of the system, aiming to provide a thermodynamic and kinetic picture of the reaction.

The computational investigation suggests that the supramolecular helicate can catalyze the reaction by binding the anionic leaving group of the substrate and consequently recruiting the resulting cationic substrate. The charge-separated supramolecular complex is then primed for the attack of the nucleophile. Although the supramolecular helicate can act as a catalyst, the charge-separated state is not strongly stabilized, suggesting that further design of the cage is needed. For this reason, we design different helicates starting from the first one investigated in this work. Relying on the previously mentioned computational approach, we explore the catalytic activity of the new candidates and we rationalize the results mainly in terms of two chemical descriptors, namely binding affinity and strain energy.

* For Abstract, see Section 1: List of Oral Contributions

Poster #480 **on-site & online**

The Functional Interplay of the ABC Transporter Pgp with its Lipid Substrates

Presenting author: **Dario De Vecchis**

Ruhr University, Theoretical Chemistry, Molecular Simulation, Bochum, Germany

Co-author/s: Lars Schäfer

The multidrug efflux pump P-glycoprotein (Pgp) is an ATP-binding cassette transporter which hydrolyzes ATP to energize the translocation of lipids and hydrophobic compounds through the plasma membrane. The protein is associated with the development of multidrug resistance and is overexpressed in a variety of cancer cells. Pgp is located in highly specialized membranes that are often rich in cholesterol and sphingolipids. However, at the atomic level, the link between this apparently consistent lipid environment and Pgp structural dynamics and function remains largely elusive. We investigated the structure and dynamics of human Pgp employing all-atom and coarse-grained molecular dynamics (MD) simulations in asymmetric multi-component lipid bilayers that mimic the hepatocyte membrane in which Pgp is expressed. We explored and compared the dynamics of two human Pgp inward-open structures, which were previously solved in detergent and nanodiscs and greatly differ in their proposed portal helices. The MD simulations visualize preferential interactions of Pgp with sphingolipids at the portal. Furthermore, they show how cholesterol and different lipid species wedge, snorkel, and in some cases even enter within the main Pgp substrate cavity. The volume and dynamics of this cavity largely differ between the two Pgp structures, and are modulated by removal of cholesterol and the presence or absence of ATP. Moreover, the MD simulations reveal that absence of cholesterol renders the nucleotide binding domains highly dynamic. Our study emphasizes the importance of the lipid environment for the dynamics of Pgp and investigates the functional role of the two different inward-open states in the context of the overall mechanism of this transporter. Finally, we will briefly discuss similarities and differences concerning protein-lipid interactions in other ABC transporters, such as MsbA.

* For Abstract, see Section 1: List of Oral Contributions

Poster #491 **on-site & online**

Unexpected Challenges in Molecular Dynamics Simulations of Large Systems

Presenting author: **Hyuntae (Henry) Kim**

Max Planck Institute of Biophysics, Theoretical Biophysics, Frankfurt, Germany

Co-author/s: Balázs Fábián, Gerhard Hummer

Molecular dynamics simulations are widely used in biophysical research. To aid non-expert users, most simulation packages provide default values for key input parameters. We found that the default setting of the neighbor list cut-off rl in the GROMACS molecular dynamics program is not sufficient to prevent various artifacts in certain large systems. Beyond an already known significant energy drift, we observed rapid oscillations in the pressure and asymmetric deformations of the box shape. In simulations of large lipid bilayers with a semi-isotropically coupled Parrinello-Rahman (PR) barostat, we found unphysical distortions of the membrane shape. We traced the cause of these different artifacts to infrequent neighbor-list updates, which resulted in systematically missed attractive Lennard-Jones interactions. For molecular systems of currently typical sizes, these effects are less pronounced. We present measures to diagnose the problem and guidelines for practitioners to avoid it, including estimates for an appropriate neighbor list cut-off rl.

* For Abstract, see Section 1: List of Oral Contributions

Poster #492 **on-site & online**

Role of Disordered Regions Beyond the Binding Motif of the Measles Virus NTAIL

Presenting author: **Gabor Nagy**

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

Co-author/s: Lillian Otteson, John Kunkel, Gerdenis Kodis, Wenwei Zheng, Christophe Bignon, Sonia Longhi, Helmut Grubmüller, Andrea C. Vaiana and Sara M. Vaiana

The Measles virus nucleocapsid is made of thousands of nucleoprotein (N) repeats, which hold the viral RNA in a helical structure. The last 125 amino acids of each N repeat (NTAIL) are intrinsically disordered and protrude radially outward from the nucleocapsid. NTAIL promotes virus replication by binding to the XD domain of the phosphoprotein P (PXD), which in turn brings the viral polymerase close to the nucleocapsid, where it transcribes and replicates the viral RNA. Only 18 amino acids of NTAIL directly bind to PXD via coupled folding and binding. The majority of NTAIL, on either side of this molecular recognition region (MoRE), remains disordered. While it has been shown that these disordered regions dampen the binding affinity, interactions involving these regions, and their possible functional role have not been identified.

* For Abstract, see Section 1: List of Oral Contributions

Poster #494 **on-site & online**

Multiscale Simulations of Molecular Recoginition by Phase Separated Mut-16: A Scaffolding Protein of Mutator Foci

Presenting author: **Kumar Gaurav**

Johannes Gutenberg University, Institute of Molecular Biology, Institute of Physics, KOMET-1, Mainz, Germany

Co-author/s: Rene Ketting, Lukas Stelzl

The RNA silencing pathway is a crucial biological process that regulates gene expression and protects the genome from foreign nucleic acids. In the nematode C.elegans, this pathway involves small RNA amplification mediated by RNA-dependent RNA polymerases (RdRPs) and the formation of perinuclear germline foci called Mutator foci. The Mutator foci are essential for the efficient processing and silencing of target RNAs. Several Mutator complex proteins, including RRF-1 and MUT-16, localize to these foci and facilitate small RNA amplification. Mut-16 acts as a scaffolding protein to recruit other Mutator complex components. Recent studies have identified the protein Rde-2, which is recruited by Mut-16 and has a prion-like N-terminal domain that may interact with the Mut-16 condensate. The C-terminal domain of Rde-2 is globular and recruits an exonuclease (Mut-7). In this study, we performed the multi-scale molecular dynamic simulations of the Rde-2/Mut-16 interaction that revealed the particular residues and type of interaction responsible for the recognition of Rde-2 to Mutator foci. The simulations were performed in three resolutions: residue-level coarse-grained simulation (HPS model), near-atomic coarse-grained simulations (Martini3), and atomistic simulation. The results showed that the recognition of Rde-2 to Mutator foci was sensitive to the protein's post-translational modifications. Further, recent studies suggest that the Mutator foci and P granules, may have liquid-like properties and form through liquid-liquid phase separation. RNA silencing in C.elegans germ cells may thus rely on multiple phase-separated compartments through which sorting, processing, and silencing of mRNAs occur. The elucidation of the molecular details of these compartments will deepen our understanding of the RNA silencing pathway and its regulatory role in gene expression.

* For Abstract, see Section 1: List of Oral Contributions

Poster #495 **on-site & online**

Gating Transitions in the MthK Potassium Channel

Presenting author: **Reinier de Vries**

Max Planck Institute for Multidisciplinary Sciences, Theoretical and Computational Biophysics, Computational Biomolecular Dynamics, Göttingen, Germany

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

We apply photo-induced electron (PET) transfer relaxation experiments of full-length NTAIL in solution to probe intra-molecular contact formation times between tryptophan (W) and cystein (C) residues introduced in different regions of the protein and under different salt and pH conditions. To better understand NTAIL dynamics, we combine PET measurements with analytical models, coarse-grained and all-atom molecular dynamics simulations, and co-evolutionary analysis. Our integrated approach identifies key, functionally important, transient non-local interactions between two regions out of MoRE. These interactions dominate the dynamics of the entire NTAIL in solution and affect the conformational preferences of the MoRE.

* For Abstract, see Section 1: List of Oral Contributions

Poster #497 **on-site & online**

Pharmacological Modulation of Trek1 Channel

Presenting author: **Edward Francisco Mendez Otalvaro**

Max Planck Institute for Multidisciplinary Sciences, Theoretical and Computational Biophysics, Computational Biomolecular Dynamics, Göttingen, Germany

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

Potassium channels are a family of ionic channels that regulates membrane potential through the permeation of ions nearly at the diffusion rate limit and with high selectivity. Particularly, TREK-1 is a channel of the subfamily of potassium channels called K2P (two-pore domain), which regulates the resting potential after a nerve impulse in mammals, keeping the membrane hyperpolarized, therefore, its pharmacological modulation is of interest, especially for treatments of hyperexcitability in neurons. The most accepted mechanism of inactivation for TREK-1 is a C-type inactivation, in which the selectivity filter (SF) is found either in a non-inactivated (canonical or conductive geometry) or inactivated (disordered or collapsed geometry) state. Recently, two modulators (namely Q6F and Q5F) have been reported, which are located in a binding site behind the SF. Besides, it is proposed that those ligands stabilize the canonical state of the SF by stiffing a loop on the top of the SF, increasing in that way the open probability of the channel. Nevertheless, other possible gates have been proposed for this same channel, and furthermore, the mechanism of action of those molecules in the loop remains open. Here, we describe, using molecular dynamics (MD) simulations, the effect of those ligands in the gates that have been proposed in the literature, as well as the main dynamics involved in the interaction of those modulators with the channel, including the approximated regions sampled by the MD and the crystal structures.

* For Abstract, see Section 1: List of Oral Contributions

Poster #503 **online**

Computational Design Optimization of Nanoparticle Based Delivery Vectors for the CRISPR/Cas9 System

Presenting author: **Alexandra Farcas**

INCDTIM, Molecular and Biomolecular Physics, Molecular and Biomolecular Technologies, Cluj-Napoca, Romania

Co-author/s: Lorant Janosi, Simion Astilean

Effective targeted gene editing can be achieved with CRISPR/Cas9 therapy, which has a number of advantages over conventional gene therapies. The key issue in adopting the CRISPR/Cas9-based technique is to design gene delivery vectors that can target mutations more specific in the genome. Furthermore, oligonucleotide-functionalized gold nanoparticles have been used to deliver CRISPR/Cas9 in vivo to treat inherited diseases such as muscular dystrophy. The delivery vectors with lower insertional mutagenesis risk should be designed based on molecular understanding of the implicated systems because current CRISPR/Cas9-Gold therapy trials are in the early stages of development. To investigate these issues, we computationally optimized such a design in two steps. First, we optimized the DNA loading on a range of GNP sizes in nanoparticle-oligonucleotide conjugates. In the second stage, we performed molecular dynamics simulations of Cas9-sgRNA complex. This study is essential in optimizing the design of CRISPR/Cas9-Gold-based delivery vehicle.

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* For Abstract, see Section 1: List of Oral Contributions

Poster #518 **on-site & online**

SUMO in Dense Protein Solutions

Presenting author: **Jan Felix Maximilian Stuke**

Max Planck Institute of Biophysics, Theoretical Biophysics, Frankfurt am Main, Germany

Co-author/s: Sören von Bülow, Gerhard Hummer

Members of the Small Ubiquitin-like Modifier (SUMO) family are small proteins with a Ubiquitin-like fold. They can be covalently attached to target proteins via isopeptide bonds similar to Ubiquitin. This posttranslational modification, called SUMOylation, can modulate the interactions, location, conformations and solubility of its substrates. It is involved in various cellular processes, one of them being the pathological aggregation of intrinsically disordered proteins (IDPs) in condensates. However, the effect of IDP SUMOylation on the properties of condensates remains elusive.

We aim to investigate the effect of SUMOylation on the properties of protein condensates with Molecular Dynamics (MD) simulations. As a first step, we study the behavior of SUMO in homogeneous dense solutions. We perform MD simulations of SUMO1, SUMO2 and Ubiquitin at increasing protein concentration and describe their interaction and diffusion properties. Preliminary analysis points to the N-terminal flexible region of SUMO, which is not present in Ubiquitin, as a key modulator of interactions and diffusion.

* For Abstract, see Section 1: List of Oral Contributions

Poster #523 **on-site & online**

Characterizing the Transport Pathway of ABCG36 Substrates Using Metadynamics

Presenting author: **Karen Odalys Torres Constante**

Semmelweis University, Department of Biophysics and Radiation Biology, Molecular Biophysics, Budapest, Hungary

Co-author/s: Markus Geisler, Tamás Hegedűs

The pleiotropic plant ABCG transporter, AtABCG36 has a role in the export of a few structurally unrelated substrates, including the auxin precursor, indole-3-butyric acid (IBA) and camalexin, which has been demonstrated to participate in defense against several pathogens in Arabidopsis. Because of these important functions, we aimed to investigate the ABCG36 substrate recognition and transport mechanisms using molecular dynamics. This transporter consists of two large transmembrane (TM) domains open towards the cytosol. When a substrate binds within the central pocket between the two TM domains, the two ATP-bound nucleotide binding domains close and the substrate is moved from the central binding pocket to the extracellular space through the Leu/Phe-valve, which is thought to participate in substrate selection. We performed umbrella sampling simulations along the CV defined as the distance between the central binding pocket and a small molecule, in the extracellular direction. Since simulations with substrates and non-substrates did not reveal rational differences in energy surfaces, we performed metadynamics simulations with IBA and camalexin including an ABCG36 variant which exhibits differences in its transport when compared to wild type. The z-component of the distance between the binding pocket and drugs was used as a CV to setup a longer path defined by the intracellular ends of the TM helices forming the binding pocket and their extracellular end delimited by the Leu/Phe valve. Our results suggest that differentiation between substrates and non-substrates does not occur at the Leu/Phe-valve.

* For Abstract, see Section 1: List of Oral Contributions

Poster #524 **on-site & online**

Structural Ensembles of Disordered Proteins and RNA from Hierarchical Chain Growth

Presenting author: **Lisa Maria Pietrek**

Max Planck Institute of Biophysics, Theoretical Biophysics, Frankfurt am Main, Germany

Co-author/s: Lukas S. Stelzl, Andrea Holla, Javier Oroz, Mateusz Sikora, Jürgen Köfinger, Benjamin Schuler, Markus Zweckstetter, Gerhard Hummer

Disordered biomolecules represent a significant fraction of the proteome in higher organisms and play vital roles in cellular processes. Over the past few decades important research in the field of intrinsically disordered proteins (IDPs) or proteins with an intrinsically disordered region (IDR) has revealed their importance in regulatory processes and their association with the development of diseases. The inherent flexibility in IDPs enables multivalent interactions, which in turn can trigger the formation of biomolecular condensates. Despite their flexible character in solution, mutations or other pathologic conditions can lead to accumulation of IDPs into aggregates or solid-like fibrils. Disorder is not limited to proteins: in particular, single-stranded RNA (ssRNA), including mRNA, can feature regions that do not fold into helical structures but remain flexible in solution.

Understanding the conformational dynamics of flexible biomolecules is crucial to get a better view on their function in health and disease. However, their flexible character makes it challenging to get an atomically detailed view from experiments alone. In the hierarchical chain growth (HCG) algorithm, we assemble fragments sampled with molecular dynamics (MD) simulations into full-length chains. The Monte Carlo assembly algorithm grows extensive ensembles of disordered biomolecules according to a well-defined ensemble. To further refine the ensemble, experimental data can be integrated during or after chain assembly. Such ensembles can complement MD simulations or serve as starting point for running independent MD simulations in parallel, from different start conformations. In applications to proteins linked to neurodegeneration, such as α-synuclein, tau and TDP-43, I showcase the value of HCG. As an outlook I highlight the potential use of HCG to sample conformations of ssRNA.

* For Abstract, see Section 1: List of Oral Contributions

Poster #525 **on-site & online**

Investigating Allostery of a Bacterial Toxin

Presenting author: **Lauren Finn**

Free University of Berlin, Department of Biology, Chemistry and Pharmacy, Molecular Dynamics, Berlin, Germany

Co-author/s: Rebecca Cummer, Bastien Castagner, Bettina Keller

Clostridioides difficile infection poses a concerning and growing public health threat, perpetuated by its primary virulence factor, Toxin B. One drugging strategy in the race to develop better treatment options aims to control an allosteric conformational change in a subdomain of Toxin B. Molecular dynamics simulations enable detailed insight on this allosteric mechanism, crucial to a rational drugging approach. Here, several strategies are combined to help sample the transition between two known conformational states. These include developing useful reaction coordinates, generating alternative conformations with AlphaFold2 and using umbrella sampling for multiple reaction coordinates.

* For Abstract, see Section 1: List of Oral Contributions

Poster #527 **on-site & online**

Mechanism of Beta-Hairpin Formation in Azochignolin

Presenting author: **Richard Zschau**

Technical University Munich, Department of Physics, T38 - Theoretical Biophysics, Munich, Germany

Co-author/s: Martin Zacharias

AzoChignolin is a photoswitchable variant of the mini-protein Chignolin that includes an azobenzene (AMPP) replacing two central loop residues. When AMPP adopts the trans-isomer, AzoChignolin remains denatured. Upon transition to the cis-isomer it folds similar to Chignolin into a beta-hairpin. Due to its small size and available experimental data on the kinetics of folding the AzoChignolin system is an excellent model system for a comprehensive analysis of its folding kinetics. Utilizing multiple 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 of cis-AzoChignolin and Chignolin. We show that while AzoChignolin mimics Chignolin's beta-hairpin structure well, the folding kinetics of the two systems are quite different. Not only different folding times but also different intermediate states are observed, particularly Chignolin is able to fold in MeOH into an alpha-helical intermediate which is impossible to form in AzoChignolin due to the central AMPP motif. The Markov models demonstrate that AzoChignolin's kinetics are generally faster, specifically when comparing the two main microfolding processes of hydrophobic collapse and turn formation. Photoswitchable loops have been used frequently to understand the kinetics of elementary steps of protein folding nucleation. However, our results indicate that intermediates and folding kinetics may differ between natural loops and photoswitchable variants.

* For Abstract, see Section 1: List of Oral Contributions

Poster #528 **on-site & online**

Comparing Correlation Measures to Study Protein Dynamics

Presenting author: **Georg Diez**

University of Freiburg, Institute of Physics, Biomolecular Dynamics, Freiburg, Germany

Co-author/s: Daniel Nagel, Gerhard Stock

Correlated motions are often essential to the functional mechanism of proteins and understanding them can already provide the key coordinates that drive a conformational change in biomolecular systems. Applications relying on correlation include, for example, a recently developed unsupervised feature preselection scheme[1] or dynamical network analysis, which aims to identify of information pathways within the protein. With that being said, different approaches to identify correlations within biomolecular systems exist, which differ in both the coordinate system as well as in the similarity measure. Thus, in dynamical network analysis, primarily the Cartesian positions of two Cα coordinates are considered, while e.g. the Markov state modeling community is more inclined to the use of internal coordinates. To compare both approaches, we investigate the notion of correlation in both coordinate systems and analyze how well linear and nonlinear similarity measures can capture the essential physical dependencies in both systems. We study the functional motion of T4 lysozyme and show that the linear correlation in the form of the absolute Pearson correlation coefficient is an excellent choice to capture dependencies in colinear data. Despite its strengths in colinear data, Pearson's correlation fails to account for perpendicular motion of atoms, which plays an important role in Cartesian coordinates. Therefore, the use of mutual information has been proposed, which is also able to capture nonlinear correlations. However, its computation is very tedious, and its normalization, especially in higher-dimensional spaces, is challenging as it relies on the delicate estimation of entropies. As a remedy, we present an extension of the popular KSG-estimator for mutual information which allows for a reliable normalization of (high dimensional) mutual information.[2]

* For Abstract, see Section 1: List of Oral Contributions

Poster #534 **on-site & online**

Modeling the Soluble and Membrane-Bound Conformations of Syntaxin 17 SNARE Proteins

Presenting author: **Tamas Hegedus**

Semmelweis University, Department of Biophysics and Radiation Biology, Membrane Protein, Budapest, Hungary

Co-author/s: Hajnalka Laczkó-Dobos, Asha Kiran Maddali, Krisztina Sebők-Nagy, Tibor Páli, Gábor Juhász

Autophagy provides degradation and recycling of various materials from macromolecules to whole organelles in eukaryotic cells. This process has a wide range of physiological and pathological roles, such as adaptation to stress and starvation, and combat cancer, neurodegeneration, and pathogens. During autophagy, cytoplasmic materials are sequestered into autophagosomes with double-membranes and transported to lysosomes for fusion, performed in a highly specific manner. We had identified a SNARE protein, STX17 required for autophagosome/lysosome fusion. This syntaxin contains N-terminal coiled-coil regions followed by a membrane bound region with two transmembrane helices, which are required and sufficient both for autophagosome localization and fusion. In spite of this transmembrane (TM) region, STX17 is also present in the cytosol and is not bound to membrane. Therefore, we aimed to characterize the soluble and membrane bound forms of STX17 using 3D-bioinformatics and molecular dynamics. The AlphaFold structure of the TM region was used for the soluble model. The TM form was modelled based on structures of TM helices with a Gly-zipper, which motif was also observed in the STX17 sequence. Microsecond long simulations were performed with the TM-form in the presence of a membrane bilayer and also with the soluble form in the presence and absence of membrane with various lipid compositions. Our results will contribute to understand the STX17's membrane association and integration processes and their dependence on negatively charged lipids.

* For Abstract, see Section 1: List of Oral Contributions

Poster #535 **on-site & online**

Structural Insights into Conformational Changes During Protein Aggregation and Refolding by Combining Theoretical and Experimental Infrared Spectroscopy of Amid Bands

Presenting author: **Marvin Scherlo**

Ruhr University, Department of Biophysics, Biomolecular Simulations, Bochum, Germany

Co-author/s: Katharina Leitmann, Marvin Rütten, Gleb Novomlinsky, Alexander Kusch, Luca Klan, Udo Höweler, Carsten Kötting, Klaus Gerwert, Till Rudack

Protein aggregation is a key event for neurodegenerative diseases such as Alzheimer disease or Parkinson. Usually, aggregation is accompanied by a secondary structure refolding from alpha helix to beta sheet. Infrared (IR) spectroscopy monitors this refolding through changes in the shape of the amid-I and amid-II bands, which are evoked by the C=O stretching and N-H bending vibrations of the protein backbone. Detailed structures of the toxic aggregates are mainly elusive and almost impossible to be resolved by structure giving experiments like X-ray crystallography, NMR spectroscopy or cryo electron microscopy. Here, we aim to reach structural insights with atomic resolution on the nanosecond time scale of aggregation processes by comparing the amid I and amid II band from experimentally measured IR spectra with theoretically calculated ones. As prove of principle we constructed small test systems reflecting different secondary structure elements and varied their length and composition to monitor the impact of structural changes on the IR spectra. We developed a method to extract the atomic contribution of each vibrational mode that enabled us to analyze and localize the impact of detailed changes in the sub-Ångstrom regime on our calculated spectra. Atomic detailed information into the aggregation processes of proteins involved in neurodegenerative diseases fosters the understanding of molecular mechanism and pathogenesis underlying such diseases.

* For Abstract, see Section 1: List of Oral Contributions

Poster #538 **online**

In Silico Identification of Potential Ligand Binding Sites of Galactokinase 1 (GALK1) to Treat Classic Galactosemia

Presenting author: **Sude Gunes**

Izmir Institute of Technology, Department of Polymer Science and Engineering, Uyar Lab - UBioModel Group, Izmir, Turkey

Co-author/s: Sabrina R. Mackinnon, Wyatt W. Yue, Arzu Uyar

Classic galactosemia is a disease associated with the mutations in the galactose-1-phosphate uridylyltransferase (GALT) gene and the deficiency of the GALT enzyme results in a higher amount of galactose-1-phosphate which causes serious concerns such as leading to liver and brain damage. On the other hand, galactokinase 1 (GALK1) is an enzyme that provides the delivery of phosphate from ATP to galactose in the Leloir pathway which includes the metabolism of galactose to glucose. In this scope, the inhibition of GALK1 can be considered as an alternative approach providing treatment of galactosemia by preventing the production of galactose-1-phosphate. Recently, inhibitors of human GALK1 (hGALK1) were found through screening, and compounds were developed through fragment-based drug discovery. In this study, the intrinsic dynamics of human GALK1 (hGALK1) was explored using a coarse-grained Elastic Network Model (ENM) and all-atom short molecular dynamics simulations, then the potential ligand binding sites of hGALK1 were predicted using an ENM-based method called Essential Site Scanning Analysis (ESSA) combined with Fpocket as well as FTMap tool. Our findings are mostly overlapping with the experimentally available crystal structures of inhibitor-bound hGALK1. Moreover, additional potential ligand binding sites were observed, which may be significant for further drug discovery studies.

* For Abstract, see Section 1: List of Oral Contributions

Poster #541 **on-site & online**

Finding Unbinding Pathways in the A1 and A2 Adenosine Receptor Combining Targeted MD and Leiden Clustering

Presenting author: **Miriam Jäger**

University of Freiburg, Institute of Physics, Biomolecular Dynamics, Freiburg, Germany

Co-author/s: Victor Tänzel, Steffen Wolf

The understanding of dynamics and free energy landscapes of ligand association and dissociation from proteins is limited by the timescales of these transitions, which is especially true for G protein-coupled receptors. Here, we enforce ligand unbinding from the A1 and A2 adenosine receptors by applying dissipation-corrected targeted MD (dcTMD) simulations [1], which enforce a moving distance constraint along a pre-chosen reaction coordinate. Clustering ligand protein contacts using MoSAIC [2], an unbiased and unsupervised method to extract coordinates corresponding to a collective motion, we reveal different ligand unbinding pathways connected to ligand-lipid interactions. Finally, free energy and friction profiles are determined along these pathways and used to retrieve (un)binding rate constants via temperature-boosted Langevin equation simulations [3].

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* For Abstract, see Section 1: List of Oral Contributions

Poster #545 **on-site & online**

In Silico Study of Protease Activated Receptor 1 (PAR1) and Thrombin Receptor Activator Peptide 6 (TRAP-6)

Presenting author: **Etienne Reboul**

Institut de Biologie Physico-Chimique, Laboratoire de Biochimie Théorique, Paris, France

Co-author/s: Antoine Taly

PAR1 is the first of the eProtease Activated Receptors (PARs), a sub-family of G protein coupled receptors, that are known to be activated by the cleavage of their N-terminal extracellular domain (Macfarlane et al., 2001).

However, the 3D structure of PAR1 has only been partially resolved experimentally (PDB entry: 3VW7) with missing parts of the cytoplasmic and extracellular domain (Zhang et al., 2012). Although there is abundant experimental data about the binding of natural tethered and synthetic ligands, to our knowledge there is no record of an experimentally resolved 3D structure of PAR1 in a complex with its ligands except for vorapaxar (PDB entry: 3VW7).

The focus of our study is twofold. First we have used ESMFold (Rives et al., 2021) to make ab initio prediction of the PAR1's 3D structure and colabfold (Mirdita et al., 2022) to predict the 3D structure of the PAR1/TRAP-6 complex. We then used unbiased all-atom molecular dynamics to study conformational differences between the holoform and the apoform of PAR1.

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* For Abstract, see Section 1: List of Oral Contributions

Poster #546 **online**

Study of The Binding Site Dynamics, Druggability and Cryptic Pocket Formation in Different Human Coronaviruses' Main Protease (Mpro)

Presenting author: **Ahmed Ezat**

Cairo University, Biophysics Department, Giza, Egypt

Co-author/s:

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 an essential protease for the viral life cycle. It catalyzes the hydrolysis of large polyproteins into mature non-structural functional proteins. So, it is a suitable target for deigning viral inhibitors. Cryptic sites are invisible pockets of the unbound protein and become visible only when binds a ligand. So, targeting such pockets offers high selectivity and specificity of the designed inhibitors to that protein and reduces the emergence of off-target binding. 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.

* For Abstract, see Section 1: List of Oral Contributions

Poster #547 **online**

Identification of Metastable States of a Large-Conductance Mechanosensitive Channel (MscL) Using Enhanced Sampling Methods

Presenting author: **Wojciech Kopec**

Max Planck Institute for Multidisciplinary Sciences, Theoretical and Computational Biophysics, Computational Biomolecular Dynamics, Göttingen, Germany

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

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. It is also known that focused ultrasound and some other factors can induce MscL activation. However, the study of this process is hampered by the fact that the mechanism of the MscL gating is poorly understood, and even the structure of the open state has not yet been characterized.

Here, we used umbrella sampling and OPES approaches to identify MscL metastable states under high membrane tension. We described a "partially open" state with an extremely low conductance (3±8 pS) and an "expanded" state with a conductance almost equal to that of the open state (> 3.2 nS). Despite the high conductance, the "expanded" state is likely not the "true" open state, since it does not satisfy all the distance restraints known from experiments. Therefore, we proposed an alternative model of the open state, and compared it with the available experimental data. The most surprising finding is that the transition between "closed" and "expanded" states breaks the five-fold symmetry typical for the MscL channel. We describe in detail the most probable transition pathway.

* For Abstract, see Section 1: List of Oral Contributions

Poster #555 **on-site & online**

Tracking Water Molecules and Ions: Investigating Channelrhodopsin Gate Opening with Molecular Dynamics Simulations

Presenting author: **Philipp Althoff**

Ruhr University, Department of Biophysics, Biomolecular Simulations, Bochum, Germany

Co-author/s: Evgenii Kurishev, Andrey Vasenin, Mathias Lübben, Udo Höweler, Carsten Kötting, Klaus Gerwert, Till Rudack

Optogenetics is a powerful method to investigate and manipulate cellular function using light-driven proteins. Usually, these proteins are microbial rhodopsins with a retinal as a chromophore. During the photocycle, photon absorption of the Retinal leads to its isomerization, which triggers further conformation and protonation-changes activating or deactivating the ion transport, respectively. To improve microbial Rhodopsins for optogenetic approaches an in depth understanding of functionalities and mechanisms is important. We developed a strategy to investigate the structure function relationships of channelrhodopsins and their conformational changes during their photocycles using a combination of molecular mechanics simulations and quantum chemical calculations. Thereby the accurate description of the ground state regarding protonation of functional amino acids and water molecule positions are essential. Therefore, we improved the standard strategy of calculating the initial protonation states and positioning of water molecules within the starting systems for molecular dynamics simulations. Based on the ground state, the activated state is reached by calculating the isomerization and processing protonation changes. To identify key functional events within the gate-opening of channelrhodopsins we developed a tool to track the interaction pattern of water molecules and ions with protein residues within molecular dynamic simulations. Structural insights and mechanistic hypothesis are validated by the combination of theoretical UV/VIS spectroscopy with experimental UV/VIS spectroscopic measurements and electrophysiological data.

* For Abstract, see Section 1: List of Oral Contributions

Poster #557 **on-site & online**

Importance of Feature Selection for Markov State Models: A Case Study on HP35

Presenting author: **Sofia Sartore**

University of Freiburg, Institute of Physics, Biomolecular Dynamics, Freiburg, Germany

Co-author/s: Daniel Nagel, Gerhard Stock

Markov state models are a powerful tool to analyze molecular dynamics trajectories based on identifying memoryless transitions between distinct conformational states (metastable states). For a deeper understanding of the biomolecular process under study, it is crucial to select states that reflect structurally different conformations, and exhibit a clear separation in time scales between fast intrastate and slow interstate dynamics. By examining the folding of villin headpiece (HP35) as a well-established example, we analyze the importance of selecting appropriate input coordinates or "features," such as backbone dihedral angles and inter-residue distances.

We find that while dihedral angles accurately describe the native basin of HP35, on the other hand tertiary contacts of the protein are better suited to capture the substructures of the unfolded region and the overall folding process itself.

By using input data that accurately reflect the basic mechanisms of the process, the resulting Markov model effectively distinguishes between states based on the input features, consistently describes the hierarchical structure of the free energy landscape, and accurately reproduces the slow timescales of the process.

* For Abstract, see Section 1: List of Oral Contributions

Poster #559 **on-site & online**

Demonstrating the Function of the Surface-Exposed Lipoprotein BtuG in Efficient B12 Transport in Association with the Outer-Membrane BtuB Protein

Presenting author: **Kalyanashis Jana**

Constructor University, School of Science, Computational Physics and Biophysics, Bremen, Germany

Co-author/s: Javier Abellon-Ruiz, Augustinas Silale, Andrew M Frey, Arnaud Basle, Matthias Trost, Bert van den Berg and Ulrich Kleinekathöfer

BtuB, a TonB-dependent transporter, is an outer membrane protein in Gram-negative bacteria that enables the active transport of cyanocobalamin (vitamin B 12) and essential nutrients (1). The protein consists of a channel with 22 β-strands combined with a large N-terminal domain, the luminal domain, folded back into and blocking the interior of the barrel. Substrate binding changes the conformational equilibrium in the Ton box as well as the luminal domain to favor an unfolded state that facilitates substrate translocation through BtuB (1–3). A newly determined BtuBG crystal structure purified from Bacteroides thetaiotaomicron has been considered for the present computational study. The BtuG, a surface-exposed lipoprotein, adopts a seven-bladed β-propeller fold. The BtuG is strongly connected to the BtuB protein through a hinge loop and can move away from BtuB in a hinge-like fashion (4, 5). We explore how the BtuG protein moves away from BtuB protein and the role of BtuG in the transport of the large B 12 molecule. To explore the B 12 acquisition mechanism, unbiased molecular dynamics (MD) along with multiple walker well-tempered metadynamics (WTMtD) simulations have been carried out. The MD simulation results demonstrate that the BtuBG protein transports cyanocobalamin through a pedal-bin mechanism: the substrate first binds to the open BtuG lid before moving to the BtuB binding site. To this end, multiple walker WTMtD simulations have been employed to determine free energy for the anticipated B 12 transport from the BtuG to BtuB active site cavity.

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* For Abstract, see Section 1: List of Oral Contributions

Poster #560 **on-site & online**

mRNA Lipid Nanoparticle Phase Transition

Presenting author: **Rainer Böckmann**

Friedrich-Alexander-Universität, Department Biology, Computational Biology, Erlangen, Germany

Co-author/s: Marius F.W. Trollmann

Crucial for mRNA-based vaccines are the composition, structure, and properties of lipid nanoparticles (LNPs) as their delivery vehicle. Using all-atom molecular dynamics simulations as a computational microscope, we provide an atomistic view of the structure of the Comirnaty vaccine LNP, its molecular organization, physicochemical properties, and insight in its pH- driven phase transition enabling mRNA release at atomistic resolution. At physiological pH, our simulations suggest an oil-like LNP core that is composed of the aminolipid ALC-0315 and cholesterol (ratio 72:28). It is surrounded by a lipid monolayer formed by distearoylphosphatidylcholine, ALC-0315, PEGylated lipids, and cholesterol at a ratio of 22:9:6:63. Protonated aminolipids enveloping mRNA formed inverted micellar structures that provide a shielding and likely protection from environmental factors. In contrast, at low pH, the Comirnaty lipid composition instead spontaneously formed lipid bilayers that display a high degree of elasticity. These pH-dependent lipid phases suggest that a change in pH of the environment upon LNP transfer to the endosome likely acts as trigger for cargo release from the LNP core by turning aminolipids inside out, thereby destabilizing both the LNP shell and the endosomal membrane.

Marius F.W. Trollmann and Rainer A. Böckmann. mRNA lipid nanoparticle phase transition. Biophys. J. 121:3927-3939 (2022) https://doi.org/10.1016/ j.bpj.2022.08.037

* For Abstract, see Section 1: List of Oral Contributions

Poster #573 **on-site & online**

Computational Structure Modelling and Dynamics of Influenza Encoded Viroporin in Host Lipid Membrane System

Presenting author: **Sehrish Jamal**

International Center for Chemical and Biological Sciences (ICCBS), University of Karachi, Third World Center for Science and Technology, H.E.J. Research Institute of Chemistry, Theoretical and Computational Chemistry Group, Karachi, Pakistan

Co-author/s: Shozeb Haider, Syed Tarique Moin

In the present time, viruses are proven to be the most dreadful entities for humankind. An elusive replication and proliferation of viruses make them very challenging to be unraveled for their mode of action. They are reported to act on multiple biological levels and control the cells' normal physiological functions for their replication by invading the host immune response systems. Viruses encode specialized small hydrophobic proteins called viroporins that alter the permeability of biological membranes by pore formation and/or self-oligomerization into Ion channels. We have studied one of the not relatively known viroporin (PB1-F2) encoded by influenza viruses which have pro-apoptotic properties keeping in view that the structural existence of this particular protein has always been a question for researchers. By using molecular modeling and molecular dynamics simulation protocols, we have addressed the possible molecular occurrence of this protein in its oligomeric forms. The simulation data were analyzed for the evaluation of the structural and dynamical properties of the protein in the realistic lipid membrane environment which provided meaningful insight into the role of the protein in mitochondrial membrane permeabilization that ultimately leads to the cell apoptosis via leakage of mitochondrial contents like cytochrome C. The current study is also expected to develop an understanding of the viroporin at the molecular level which could aid to obtain a clear picture of the infection life cycle and therefore in the development of potent therapeutics against the virus.

* For Abstract, see Section 1: List of Oral Contributions

Poster #576 **on-site & online**

Exploration of Ion Permeation in the Gramicidin A Channel Using a Charge Scaling MD Approach

Presenting author: **Ricarda Kuntze**

Max Planck Institute for Multidisciplinary Sciences, Theoretical and Computational Biophysics, Computational Biomolecular Dynamics, Göttingen, Germany

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

Gramicidin A is a small, 15 amino acid long helix-forming peptide. In a membrane environment, gramicidin A can form into a membrane-spanning helix dimer that acts as a cation-selective ion channel. Due to its simple structure and experimentally well known functional properties, gramicidin A is a popular model channel for studying ion permeation. However, accurately capturing its high measured ion flux has long been a long-standing issue for classical molecular dynamics (MD) simulations. Recently, low free energy barriers that better match experimental estimates have been predicted by polarisable force fields. Here, we test an alternative approach based on charge scaling in classical, fixed-charge atomistic MD simulations, with the goal of achieving conductances comparable to experiment while minimising computational costs. We see a large improvement in simulated currents, as they are within an order of magnitude of experimental measurements. Further, we discuss the influence of other parameters, such as temperature, membrane voltage and cation type on ion permeation. In general, charge scaling offers a simple approach to gain further insights into the gramicidin A permeation mechanism, particularly into the influence of the channel dynamics.

* For Abstract, see Section 1: List of Oral Contributions

Poster #581 **on-site & online**

Peptide Binding in MHC Receptors

Presenting author: **Simone Goeppert**

Technical University Munich, Molecular Dynamics, Munich, Germany

Co-author/s: Martin Zacharias

Major Histocompatibility complexes class I (MHC) proteins enable the immune system to analyze the infectious status of cells. The MHC class I proteins bind antigenic peptides located in the cell and present them to the immune system on the cell surface. Effective surface presentation requires binding of high affinity peptides which is achieved by a sophisticated peptide loading and editing process requiring the chaperone proteins tapasin and TAP-binding protein related (TAPBPR). Available crystal structures of TAPBPR and tapasin in complex with MHC class I molecules indicate the molecular details of the interaction geometry. Using extensive molecular dynamic (MD) simulations of tapasin and TAPBPR complex structures in the presence and absence of low- and high-affinity peptides we have investigated the mechanism of peptide loading and editing. It allows us to study the role of specific recognition elements for the chaperone process and of conformational changes observed in class I molecules upon chaperone binding. Comparative simulations on tapasin vs. TAPBPR complexes reveal differences in the role of recognition elements for the loading process which may relate to different functional roles.

* For Abstract, see Section 1: List of Oral Contributions

Poster #582 **online**

Conformational Selection in the CBD Domain of Cre Recombinase

Presenting author: **Marco Ramírez**

Universidad Autónoma del Estado de Morelos, Dinámica de Proteínas, Grupo de dinámica de proteínas y ácidos nucleicos, Cuernavaca, Mexico

Co-author/s: Dra. Nina Pastor

During site-specific recombination tyrosine recombinases promote the scission, insertion, and recombination of specific DNA sequences. The Cre/loxP system from P1 bacteriophage promotes viral DNA circularization after infection and equitable plasmid assortment during cell division. It acts by forming a tetramer (intasome) in which Cre monomers are bound in a head-to-tail fashion to a half loxP site, alternating between active and inactive conformations. Despite knowledge of the recombination mechanism and strand exchange order, information regarding target selection and intasome assembly is still missing. We used molecular dynamics simulations (MD) to assess the conformational flexibility of the CBD domain of Cre recombinase. The starting seeds for MD were structures with PDB id 1q3u (an intasome) and 7rhy (a Cre monomer bound to a loxP half-site); these structures vary in the position of helix A. We simulated four replicas for each system for 5 microseconds in an explicit solvent model (TIP3P) with the software GROMACS using CHARMM36m at 300K and 1 atm. Van der Waals interactions were calculated using a 1.2 nm cutoff and PME for electrostatics, with a 4 fs timestep. Our results show that helix A can switch from an intasome-like to a monomer-like conformation, passing through distinct intermediate and unfolded states. These results suggest that the position of helix A is selected concomitantly with establishing monomer-monomer interactions during intasome assembly. Also, the flexibility of helix A could help to interpret NMR data in which the signals for this helix are missing.

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* For Abstract, see Section 1: List of Oral Contributions

Poster #583 **on-site & online**

GROMACS Meets FMM - The Path to Highly Scalable Constant pH Electrostatics

Presenting author: **Bartosz Kohnke**

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

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

The efficient calculation of long-range Coulombic interactions is a major challenge in molecular dynamics (MD) simulations. Currently, performance improvements are primarily achieved utilizing parallelization, typically on multi-node, multi-core multi-GPU clusters. As the number of nodes increases, parallel scalability becomes the most critical requirement to achieve optimal performance. As we approach the scalability limits of the prevailing particle mesh Ewald (PME) method, the development of a better scaling method has become essential. Therefore, we implement a GPU-based fast multipole method (FMM) to efficiently evaluate protein electrostatics and enable simulations of biomolecules on future highly parallel computers. Additionally, our GPU FMM implementation facilitates the study of biomolecules in complex chemical environments by modeling dynamic protonation via the lambda-dynamics constant pH method.

Currently, our FMM implementation runs on a single GPU and outperforms PME for simulation systems that are large but contain a small number of atoms (such as water droplets or aerosol systems). Our next step is to parallelize the FMM across multiple nodes and GPUs to enable higher performance for larger system sizes. Our implementation can be used as an independent electrostatics solver or as a PME replacement in the GROMACS MD simulation package.

* For Abstract, see Section 1: List of Oral Contributions

Poster #586 **on-site & online**

Reinforcement and Competition Between RNAPolII-Enhancer-Promoter Contacts and Cohesin-CTCF Loop Extrusion

Presenting author: **Mariano Barbieri**

University Medicine Göttingen, Institute of Pathologie, Translational Epigenetics Laboratory, Göttingen, Germany

Co-author/s: Shu Zhang, Nadine Übelmesser, Argyris Papantonis

Genome transcription regulation in eukaryotes is a highly complex and yet highly coordinated process in space and time. Often, distal regulatory actors have to co-localize during the normal expression program, forming long-range loops of chromatin. RNAPolII-driven transcription condensate formation or cohesin-CTCF loop extrusion have been increasingly inspected as important mechanisms of loop formation. Nevertheless, a comprehensive mechanistic picture is still missing. To this aim, perturbation experiments, e.g. where a certain actor is removed from the system, have the highest predictive power for model testing. What happens to chromatin long range architecture if we remove RNAPolII? By using a human cell line that allows for the auxin-mediated degradation of the largest RNAPII subunit, RPB1, and with the aid of numerical simulations of polymer physics, we show that the new distribution of loops observed hints to a complex interplay between transcription and loop extrusion mechanisms.

* For Abstract, see Section 1: List of Oral Contributions

Poster #588 **online**

ReverseDock: A Web Server to Dock a Single Ligand to Multiple Protein Targets

Presenting author: **Mehmet Ali Öztürk**

University of Freiburg, BIOSS and Institute of Biology II, Molecular and Cellular Engineering Group, Freiburg, Germany

Co-author/s: Fabian Krause, Karsten Voigt, Barbara Di Ventura

Several platforms exist to perform molecular docking to find ligand binders to a specific protein target from a library of ligands. Docking of a single ligand to various targets is, however, currently offered by very few web servers limited to a predefined set of human proteins from which the proteins of interest might be excluded. Here we present ReverseDock, a web server specifically designed to allow users with little to no computational expertise to dock a ligand to proteins from several model organisms involved, for instance, in a particular biological process or localised to a certain cellular compartment. Users submit a ligand structure and a list of protein targets in terms of either UniProt IDs or GO term-based filtered outputs of the AmiGO 2 tool. The submitted ligand is then docked to the AlphaFold-predicted 3D structures of the target proteins by using the established docking program AutoDock Vina. The docking results, ranked according to binding energies, are visualised through an interactive graphical interface. With its user-friendliness and no prerequisite of computational structural biology knowledge, ReverseDock will facilitate the prediction of ligand binding to entire families of proteins, as well as potential off-target events, which are of interest in drug design and repurposing.

Access: https://reversedock.biologie.uni-freiburg.de/

* For Abstract, see Section 1: List of Oral Contributions

Poster #590 **on-site & online**

Role of Receptor-Receptor Interaction as Checkpoint in Immune Signaling

Presenting author: **Cristian Popov**

Friedrich-Alexander-Universität, Department Biology, Computational Biology, Erlangen, Germany

Co-author/s: Matthias Pöhnl, Michaela Seeling, Falk Nimmerjahn, Rainer A. Böckmann

Fc receptors are single-pass transmembrane proteins, expressed on the surface of innate immune effector cells, that bind the so-called Fc portion of antibodies. Immune effector cells are regulated by a precise interplay of activating and inhibitory receptors, which, upon ligand binding, contribute either a positive or a negative signal to the pro-inflammatory response. Malfunctioning of these mechanisms can lead to overactive immune cells and the destruction of healthy tissue known as autoimmune response. In human, the only inhibitory Fcγ receptor (Fc receptors that bind specifically to immunoglobulin G (IgG)) is FcγRIIb whose binding to IgG prevents an inflammatory response. Activated by IgG binding to the extracellular domain of FcγRIIb, the immunoreceptor tyrosine-based inhibitory motif (ITIM) located within the soluble intracellular domain is phosphorylated by Src kinases, upon which it exerts its inhibitory function. Here, we used combined coarse-grained and atomistic molecular dynamics simulations and experimental studies to investigate IgG binding to FcγRIIb. We show that the Dectin-1 receptor modulates the capacity of FcγRIIb to interact with IgG via rearranging FcγRIIb conformation and membrane clustering, suggesting that Dectin-1 acts as a co-inhibitory checkpoint modulating FcγRIIb inhibitory function [1]. Furthermore, we investigate how competitive binding of the FcεR1γ-dimers to activating Fc receptors may modulate immune cell activation. [1] Seeling et al. 2023. in press.

* For Abstract, see Section 1: List of Oral Contributions

Poster #591 **on-site & online**

How a Stretching Force Differently Destabilizes Chemical Bonds on a Protein Backbone

Presenting author: **Daniel Sucerquia**

Heidelberg Institute for Theoretical Studies (HITS), Department of Physics, Molecular Biomechanics, Heidelberg, Germany

Co-author/s: Frauke Gräter

When subjecting a protein chain to extreme pulling forces, bonds in the stretched backbone ultimately break. Predicting such ruptures can help to understand failure of protein materials. As a most simple assumption, a protein backbone can be considered as a series of harmonic springs each of which carries the same force, and they only differ in their thermodynamic stability. However, proteins are more complex than that and force will distribute across the various degrees of freedoms in the peptide, largely depending on the chemical environment.

We here study the changes of energy stored in the degrees of freedom of molecules at quantum level of accuracy using JEDI (T. Stauch and A. Dreuw, Chem. Rev. 116, 2016). JEDI assesses the distribution of energies in stretched molecules using density functional theory and a harmonic approximation around optimized conformations. We so far have tested this method in chains of amino acids consisting of alanines, glycines, and prolines, and their combinations. We observe a linear increase in energies per degree of freedom including bonds, angles, and dihedrals, during stretching, and proline to show an energy distribution distinct from the other amino acids due to the ring structure. Data from QM and JEDI calculations of a large set of small peptides will aid to predict the energy distribution in larger systems using Machine Learning, for example for allowing bond rupture during classical Molecular Dynamics simulations.

* For Abstract, see Section 1: List of Oral Contributions

Poster #593 **on-site & online**

One Ring to Rule Them All: Lugdunin's Disruptive Effects

Presenting author: **Marius F. W. Trollmann**

Friedrich-Alexander-Universität, Department Biology, Computational Biology, Erlangen, Germany

Co-author/s: Dominik Ruppelt, Claudia Steinem, Rainer Böckmann

Antimicrobial resistance represents a growing threat to global public health, underscoring the urgent need for novel strategies to counteract the spread of multi-resistant bacterial strains. Antimicrobial peptides (AMPs) have emerged as a promising alternative to common antibiotics for inhibiting bacterial growth without inducing new forms of resistance. Recently, the cyclic peptide lugdunin was isolated from nasal Staphylococcus lugdunensis and has shown a strong antimicrobial activity against several Gram-positive bacteria [1]. Lugdunin consists of six D,L-amino acids and a thiazolidine moiety.

While maintaining membrane integrity, lugdunin was shown to enable proton translocation across the membrane [2]. However, the mechanistic mode of action of lugdunin with membranes is still poorly understood. Here, we used atomistic molecular dynamics simulations of different lugdunin complexes to study its differential interaction with bacterial and mammalian cell membranes.

[1] Zipperer et al. 2016. Human commensals producing a novel antibiotic impair pathogen colonization. Nature. 535:511–516.

[2] Schilling et al. 2019. Synthetic Lugdunin Analogues Reveal Essential Structural Motifs for Antimicrobial Action and Proton Translocation Capability. Angew. Chem. Int. Ed Engl. 58:9234–9238.

* For Abstract, see Section 1: List of Oral Contributions

Poster #596 **on-site**

From the Integrative Atomic Resolution Ensembles of Disordered Proteins to Simulations of Phase Separated Condensates

Presenting author: **Lukas Stelzl**

Johannes Gutenberg University & Institute of Molecular Biology (IMB), Institute of Physics & Faculty of Biology, KOMET1, Mainz, Germany

Co-author/s: Lisa M. Pietrek, Xiaofei Ping, Andrea Holla, Mateusz Sikora, Juergen Koefinger, Dorothee Dormann, Benjamin Schuler, Markus Zweckstetter, Gerhard Hummer

Dysregulation of biomolecular condensates of disordered proteins such as tau and TDP-43 is a driver of neurodegenerative diseases. A detailed understanding of the structure and dynamics of disordered proteins in dilute and condensed states will help to elucidate 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 limitation, we adopt a hierarchical approach, combining a highly accurate description of local structures with efficient sampling of possible global structures. We show how to make use of experimental data in the modeling of disordered proteins with a Bayesian formalism, overcoming the problem of exponentially varying weights in the ensemble refinement of long-chain polymeric molecules with importance sampling. Our atomic-resolution ensembles of dilute α-synuclein and tau agree well with small-angle X-ray scattering and NMR data, which were not used to generate the ensembles. For tau we find that pathogenic P301 mutations shift the ensemble towards locally more extended structures, which may be more aggregation prone. Using the same framework we simulate phase-separated condensates not just of tau but also of the neurodegeneration-linked protein TDP-43 and complement coarse-simulations of the phase behavior of TDP-43. Combining coarse-grained and atomistic simulations we demonstrate how phosphorylation gives rise to an anti-aggregation effect that may help to counteract disease progression.

* For Abstract, see Section 1: List of Oral Contributions

Poster #606 **online**

Computational Analysis of the Interaction of HIV-1 Capsid and Nanobody Complex Structure with a Potential for Diagnostic Applications

Presenting author: **Seref Berk Atik**

Izmir Institute of Technology, Department of Bioengineering, HTS Lab, Izmir, Turkey

Co-author/s: Şeref Berk Atik, Arzu Uyar and Humeyra Taskent Sezgin

HIV infection is still an active pandemic in the world. Since this highly mutagenic virus was identified, over 40 million people have died of HIV infection. Currently, 38.1 million people are infected with HIV. After a person is infected, the viral genome integrates itself into the host cell genome. The infected person carries the virus their whole life and can transmit the virus to other people through bodily fluids. Since there is no cure for HIV yet, the World Health Organization's recommendation is to diagnose infected people early through widespread screening to control the spreading of the virus. Therefore, there is still a need to develop practical, sensitive diagnostic tests especially suitable for field use for HIV infection diagnosis.

In this study, the interaction between HIV-1 capsid (CA) protein, the first antigen that appears in the blood in the acute phase of HIV infection, and a nanobody (Nb, a single domain antibody) that is known to bind to capsid is analyzed at the molecular level by computational methods. Since the crystal structure of HIV-1 CA binding-Nb is not known, first, all-atom models of the Nb structure were built by homology-based and AI-based tools (SwissModel, trRosetta, Robetta, AlfaFold2), and promising models were selected. In the second step, HIV-1 capsid-nanobody complex structures were generated using docking, then their stability and native-likeness were evaluated using conventional molecular dynamics simulations. We believe that understanding the HIV-1 capsid-nanobody complex would generate preliminary data for the development of a plasmonic immunosensor.

* For Abstract, see Section 1: List of Oral Contributions

Poster #607 **on-site & online**

Energetics and Permeation of Small Molecules Used for 3D-Laser Printing Across Biological Lipid Bilayers

Presenting author: **Camilo Aponte-Santamaría**

Heidelberg Institute for Theoretical Studies (HITS), Molecular Biomechanics, Heidelberg, Germany

Co-author/s: Lucas Diedrich, Matthias Brosz, Tobias Abele, Salome Steinke, Frauke Gräter, Kerstin Göpfrich

3D bioprinting describes a collection of techniques that use small molecules (bioinks) to create macroscopic, biocompatible, and highly-precise three dimensional structures, with promising applications in tissue engineering, mechanobiology and bottom up synthetic biology. The selection of suitable bioinks represents a crucial step in 3D bioprinting. While some applications, e.g. 3D printing inside artificial cells, require the utilized molecules to permeate through biological lipid membranes, others need to exclude the molecules from living cells due to potential cytotoxic effects. In both cases, the interaction of this type of molecules with biological lipid bilayers is of paramount importance and little is known about it. In particular the energetic costs and rates of membrane permeation of these small molecules remain unknown, this in part because the experimental assessment of these properties is extremely difficult. Here, we elucidate the free-energy, diffusion coefficient and permeability across biological lipid bilayers of a large set of photo-resist molecules in silico, by applying equilibrium, umbrella-sampling, and non-equilibrium free-energy based molecular dynamics simulations. We obtained partition coefficients that correlate well with experimental data and help classifying the photoresist according to their propensity to reside in the oil phase of the lipids. The obtained energy landscapes reveal the energetic barrier the photo-resists must overcome in order permeate the membrane along with preferential localization sites inside the bilayer. By combining diffusion coefficient and free energy profiles, permeability coefficients were obtained, revealing a broad range of permeation for the photo-resists, spanning almost 8 orders of magnitute, which correlates well with the oil/water partition coefficients, i.e. following Overton's rule. Overall, our data provide the molecular basis of the interaction of bioinks with biological membranes. By complementing experiments, our computational approach will help to rationally select suitable bioinks for different 3D bioprinting applications.

* For Abstract, see Section 1: List of Oral Contributions

Hybrid Workshop, April 28-29, 2023
"COMPUTER SIMULATION AND THEORY OF MACROMOLECULES"

Poster #774 **online**

DNA-Repair Mechanisms: Molecular Simulations and Computational Alchemy

Presenting author: **Frank Beierlein**

Friedrich-Alexander-Universität, Erlangen National High Performance Computing Center (NHR@FAU), Erlangen, Germany

Co-author/s: Senta Volkenandt, Petra Imhof

The DNA repair protein thymine DNA glycosylase (TDG) removes mispaired or damaged bases, such as oxidized methylcytosine, from DNA by cleavage of the glycosidic bond between the sugar and the target base flipped into the enzyme's active site. The enzyme is active against formyl-cytosine and carboxyl-cytosine, whereas the lower oxidized hydroxymethyl-cytosine and methyl-cytosine itself are not processed by the enzyme. To investigate the substrate specifity of TDG, we used extensive molecular dynamics simulations and thermodynamic integration of TDG complexed to DNA carrying one of four different (oxidized) methyl-cytosine bases methyl-cytosine (mC), hydroxymethyl-cytosine (hmC), formyl-cytosine (fC), or carboxyl-cytosine (caC), in extra- and intrahelical conformation, and in their amino- and imino-tautomeric forms. Our results indicate that discrimination of the oxidized methyl-cytosines does not take place in the initial complex formation before the base has been flipped out into the active site, and that imino-tautomers do not play a role in substrate recognition at this stage. For the extrahelical complexes, we observe a more favorable binding affinity of the higher oxidized forms, fC and caC, compared to the nonsubstrate bases hmC and mC. Despite rather comparable, reaction-competent conformations of the flipped bases in the active site of the enzyme, more and stronger interactions with active site residues account for the preferred binding of the higher oxidized bases. Overall, our computational results indicate that the enzyme discriminates the different oxidation forms of methyl-cytosine at the formation of the extrahelical complexes, and possibly also at a later chemical step.

[1] F. Beierlein, S. Volkenandt, P. Imhof, J. Phys. Chem. B 2022, 126, 1188.

(DOI: 10.1021/acs.jpcb.1c09896)

[2] S. Volkenandt, F. Beierlein, P. Imhof, Molecules 2021, 26, 5728.

(DOI: 10.3390/molecules26195728)

* For Abstract, see Section 1: List of Oral Contributions

Poster #810 **online**

Molecular Dynamics Study of Interactions between Nanoplasics and Lipid Membranes

Presenting author: **Anna Stachowicz-Kusnierz**

Jagiellonian University, Faculty of Chemistry, Department of Theoretical Chemistry, Group of Thermodynamics and Dynamics of Chemical Reactions, Krakow, Poland

Co-author/s: Jacek Korchowiec, Franciszek Włodek

Plastic pollution has been recognized as a serious problem in terms of environmental protection and public health. Micro- and nanometer-sized plastic particles are ubiquitous in water, soil, and air. In the latter case they are become part of air pollution. Particles with diameter below 2,5 µm, when inhaled, penetrate the lungs, and may enter body tissues. Lipid membranes form barriers which foreign substances must cross before entering the body. In lungs, the first such barrier is the lung surfactant (LS) system. It is a surface film spread on alveolar subphase covering pulmonary epithelial cells. Its main function is to reduce surface tension in lungs. On the microscopic level LS has a complex 3D structure composed of a monolayer on the phase boundary and multilamellar lipid reservoirs associated with the surface. After crossing the LS system, pollution particles meet cellular membranes which also have to be crossed.

In this study, interactions between model lipid monolayers and bilayers with model nanoplastics (NP) was examined by means of classical all-atom molecular dynamics simulations. NPs of polyethylene, polypropylene, polystyrene, and polylactic acid with varying size were introduced into phospholipid membranes. Varying composition of the monolayers and bilayers was used in order to mimic different environments, i.e. LS vs epithelial cells' cellular membrane. Adsorption processes, NPs affinity towards lipids, the particle's fate in lipid environment, the impact of NPs adsorption on membrane structure, and vice versa were analyzed.

* For Abstract, see Section 1: List of Oral Contributions