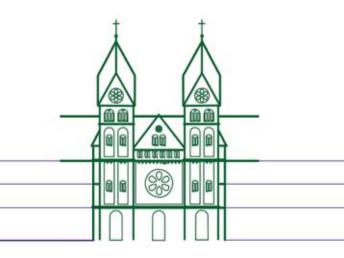# COMPUTER SIMULATION AND THEORY
OF MACROMOLECULES

Hünfeld, April 19-20, 2024, Hybrid

Section 1:

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"COMPUTER SIMULATION AND THEORY OF MACROMOLECULES"

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Hybrid Workshop, April 19-20, 2024
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oral #126   **on-site**

How Can Cell Penetrating Peptides Enter via Membrane Fusion?

Presenting author: **Pavel Jungwirth**

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Co-author/s: -

We aim at elucidating the molecular mechanism of passive membrane crossing of cell penetrating peptides, such as oligoarginines, using a combination of fluorescence and cryoelectron microscopies and molecular dynamics simulations. Recently, we have shown using atomistic simulations that calcium dications can induce membrane fusion in vesicles rich in phosphatidylethanolamine. Moreover, we have shown that arginine-rich peptides are similarly fusogenic and have suggested that from mechanistic point of view the passive membrane penetration of arginine-rich peptides may be analogous to calcium-induced membrane fusion. Here, we employ fluorescence and cryo-electron microscopies on vesicles and cells combined with simulations to elucidate the molecular details of passive cell entrance of arginine-rich peptides. The experimental results point to a hitherto unexplored mechanism involving induction of membrane multilamellarity, potentially followed by a process analogous to calcium-induced membrane fusion.

oral #154   **on-site**

Investigation on the Protein Dynamics at Extreme Temperatures

Presenting author: Beatrice Caviglia

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Thermostability of cells and their components is a current research focus. In specific, the link between the stability of proteins, the most abundant and less stable macromolecules of a cell, and the process of temperature induced cell death is not completely elucidated, but poses a fundamental question from a theoretical, biotechnological, and clinical view [1], [2]. A recent work, which investigated the dynamical profile of the proteins in the E. Coli cell, a mesophilic bacterium, and the rate of unfolded proteins at the cell death temperature revealed a dynamical catastrophe around the cell death temperature caused by only 10% of the proteins [3]. Based on these findings, in this project we use all-atoms molecular dynamics simulations (MD) in combination with neutron scattering measurements (NS) to investigate the dynamics of the proteins in extremophilic bacteria and to reveal whether it is a small set of proteins that unfolds. In this occasion, the aim is to show how MD simulations can be used to model the dynamics of the proteins and to quantify the number of unfolded proteins at the cell death temperature by incorporating NS measurements. Different dynamical aspects that have been revealed so far for the extremophilic bacteria, A. Aeolicus and P. arcticus using MD simulations and NS experiments, such as the global diffusion coefficient and the mean square displacement of the proteins of the two bacteria, will be demonstrated.

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oral #281 **on-site**

Accessing the Conformational Space of Viral Protein Models by GōMartini 3 Approach

Presenting author: Gustavo Enrique Olivos Ramirez

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Co-author/s: Luis F. Cofas-Vargas, Adolfo B. Poma

The conformational space of proteins can be characterized by structural analyses, dynamical contact map determination, and free energy landscape; which are typically calculated in the µs timescale by all-atom molecular dynamics (MD) simulation. However, longer timescales are still prohibited to all-atom MD, yet they are necessary to assess the quality of protein models. In contrast, coarse-grained (CG) MD has the advantage of expanding this scales by more than 2 orders of magnitude, reducing the computational cost at the expense of losing information on the specific interactions between atoms. The GōMartini approach [1] is an alternative tool to circumvent this limitation, and, in its recent implementation, it employs virtual sites near the Cα -atom positions in the Martini 3 force field [2]. This approach requires the determination of a contact map that includes the most relevant interactions between residues. In this, study we apply this CG method to increase our understanding of the long-time dynamics of a protein model with no a priori deposited experimental structure. Here, we focus efforts to describe the telomere-binding protein from Monkeypox virus (MPXV-TBP) that is an essential virosomal protein for virus multiplication in other analogous viruses, emerging as a promising pharmaceutical target. Hence, we performed an exhaustive exploration (i.e. timescale of few hundreds of µs) of the conformational space of MPXV-TBP (UniProtKB ID: Q8V518) under GōMartini 3 approach. Long-time dynamics comprises CG simulations for three representative models: i) AlphaFold v.2, ii) homology models, and iii) frames retrieved from unbiased all-atom MD simulation. Our study unveils major differences between all three models and may suggest ways
for new strategies in rational drug design aimed at viral proteins.

oral #319   **on-site**

Exploring the Conformational Landscape of a Class A G Protein-Coupled Receptor with Biased Molecular Dynamics Simulations and Markov State Modeling

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G protein-coupled receptors (GPCRs) are key players in signal transduction and as such are involved in most physiological and pathological processes. As GPCRs are the most represented protein family among membrane receptors, they are responsible for cellular responses to a variety of different stimuli, including hormones, neurotransmitters, and exogenous substances. It is estimated that one-third of approved pharmaceutical drugs target GPCRs [1]. To date, computer-aided drug design and discovery applied to GPCRs are largely based on their experimental structures obtained from cryogenic electron microscopy (cryo-EM) or X-ray crystallography. However, these techniques only capture the receptors in their lowest energy conformation under specific experimental conditions, whereas it is widely recognized that the activity of GPCRs spans a broad spectrum of structurally and functionally distinct and transient states in equilibrium [2]. To bridge this gap, we aim to capture this highly diverse conformational landscape and shed light on its modulation by different ligands (agonists, inverse agonists, antagonists). Our model system is the growth hormone secretagogue receptor (GHSR-1a), which belongs to the subfamily of class A GPCRs and controls growth hormone secretion, food intake, and reward-seeking behaviors upon interaction with the neuro-endocrine peptide hormone ghrelin [3]. Taking advantage of the huge amount of structural data in the field, we performed a principal component analysis (PCA) of all class-A GPCR structures available in the Protein Data Bank (PDB), based on the assumption that the collective motions among the protein family are conserved. We used the amplitudes of displacement along the first eight eigenvectors as collective variables for well-tempered meta-dynamics simulations combined with a bias exchange scheme. We show that 1 μs of accumulative simulation time along each principal component is sufficient to sample the collective motions of the receptor in the eight-dimensional space. We leveraged the models generated by meta-dynamics as starting points for additional classical (unbiased) MD simulations whose a posteriori analysis using a Markov state model provides insights into the dynamical transitions within the conformational landscape of GHSR depending on the bound ligand.

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oral #326   **on-site**

Condensate Coexistence in Gene Transcription: Molecular Dynamics Insights

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The formation of distinct phase-separated condensates of biological macromolecules underpins specific regulation in cells. Here we elucidate under what conditions phase-separated condensates can regulate biochemical processes by providing distinct chemical environments with particle-based multi-scale simulations. As a prototypical example, we study the disordered C-terminal domain of RNA polymerase II (CTD), which in experiments has been found to form condensates under both unphosphorylated and phosphorylated (pCTD) states. CTD condensates have been proposed to underpin transcription initiation, while pCTD condensates may support transcription elongation. A better understanding of the molecular driving forces of CTD phase separation will provide insights into how CTD and pCTD condensates can regulate transcription initiation and elongation. Combining nuclear magnetic resonance (NMR) spectroscopy and atomistic molecular dynamics to generate conformational ensembles using a Bayesian formalism, illustrates the significance of interactions involving tyrosine, notably tyrosine-proline contacts driving the phase separation of CTD. In vivo experiments in C. elegans show that CTD is more prone to condensation at higher temperatures (30°C) than at lower temperatures (5°C). However, it has remained unclear whether CTD and pCTD condensates would mix when coexisting or remain as distinct chemical environments; either as multi-phase condensates or by forming entirely separate condensates. Computing surface tensions from coarse-grained molecular dynamics simulations we establish under what conditions they remain coexist either as multi-phase condensates or by forming entirely distinct condensates. Our findings indicate that the two phases associated with transcription initiation and elongation constitute distinct chemical environments, which modulate chain conformations. These condensates facilitate the selective recruitment of other biomolecules, as demonstrated with FUS. Comparisons with atomistic reference simulations and experimental data highlight that our simulations capture the essential elements of CTD interactions.

oral #327   **on-site**

Simulation of Ion Mobility Spectrometry Experiments

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Co-author/s: Juan Luis Restrepo-López, Christoph Wichmann, Jürgen Cox, Helmut Grubmüller

Mass spectrometry based proteomics is becoming an invaluable analysis tool of complex samples like human cell lysates and allows the identification and quantification of thousands of proteins. To enhance the coverage and accuracy of complete proteomes the digested proteins are initially separated with HPLC and in latest devices additionally by trapped ion mobility spectrometry (TIMS). Ion mobility spectrometry enables differentiation of peptides based on their mass, size, shape and charge distribution. However, a deeper understanding of the peptide conformation in the low pressure environment of the drift tube would help the interpretation of the measurement results and foster instrument development. Therefore, we carried out molecular dynamics simulations of a model peptide in low pressure air (2.7 mbar). Simulation parameters were carefully adjusted to reproduce the experimental conditions as close as possible. Drift speed obtained from simulations show a decent agreement with experimental measurement e.g. 60 m/s versus 78 m/s, respectively.

oral #336   **on-site**

Atomistic Mechanism of Copper Transfer to Plant Receptor ETR and Structural Receptor Dynamics after Binding of Ethylene and 1-Methylcyclopropene

Presenting author: Lisa Sophie Kersten

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Co-author/s: Stephan Schott-Verdugo, Holger Gohlke

The gaseous plant hormone ethylene is a small molecule recognized for its role in triggering fruit ripening. Its interaction with the plant receptor ETR1 (ethylene response 1) within the transmembrane sensor domain (TMD) is crucial for this effect [1]. The TMD obtains its high affinity and specificity for the chemically simple ethylene molecule through an essential copper cofactor, which also binds in the TMD. To date, established pathways elucidate the transport of copper from the cell's plasma membrane to the ER membrane-bound ETR1 by the chaperones ATX1, CCH, and RAN1. These chaperones are characterized by a shared structure featuring a ferredoxin-like fold and a copper-binding motif [2]. Despite this knowledge, a comprehensive understanding at the atomistic level of the interactions between the chaperones and ETR1 is still lacking. Here we present preliminary interaction models derived from coevolutionary and structural data, coupled with protein-protein docking. It is known that ETR1 bound to ethylene undergoes conformational changes, leading to the failure of downstream target activation and initiation of fruit ripening. Many strained alkenes, such as 1 methylcyclopropene (1-MCP) are effective antagonists of ethylene responses by targeting the same binding site [3]. However, it remains elusive, how ethylene binding deactivates ETR1 and why 1-MCP functions as an ethylene antagonist. Here, we provide initial insights into how ethylene deactivates, and how 1-MCP maintains, ETR1 activity. Leveraging our model of the ETR1 TMD [4,5] and employing free ligand diffusion simulations, we constructed an ETR1:Cu(I):ethylene TMD model that aligns with our characterization of the ethylene binding site [6]. Additionally, we developed parameters of ethylene or 1-MCP binding to Cu(I) by applying a bonded model. Both the distances and force constants obtained indicate that 1-MCP interacts more strongly with copper than ethylene. The obtained trajectories of the ethylene-bound ETR1 TMD suggest directional movements of amino acids known to be associated with ethylene binding or signal transduction. These movements are less pronounced or absent in the unbound- or 1-MCP bound states. Overall, these studies provide initial insights into the atomistic mechanism of copper transfer, how ethylene binding affects ETR1 structural dynamics, and how antagonists, such as 1-MCP, maintain ETR1 activity and might give a perspective of the structural dynamics of full-length ETR1 at the atomistic level.

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oral #339   **on-site**

Effects of Charge Scaling on Potassium Channel Simulations, Conductance, Ion Occupancy, Voltage Response, and Selectivity

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Potassium channels are widely distributed in many types of organisms. They permeate potassium ions at high rates (~100pS). Potassium channels achieve high efficiency and selectivity by a conserved selectivity filter with four adjacent potassium-binding sites. Molecular dynamics simulations can provide a detailed mechanism for this sophisticated ion permeation. However, there are clear inconsistencies between the molecular dynamics prediction and experiments. Firstly, the ion occupancy of the selectivity filter is lower than expected (~2.5 compared to ~4 from X-ray crystallography). Second, the conductance is an order of magnitude lower than what is measured in single-channel electrophysiology experiments. This discrepancy is likely because the force fields typically used in MD simulations do not account for polarization. One proposed force field modification is the ECC (Electronic Continuum Correction), which scales down the charge to introduce the polarization in a mean-field way. When ECC is applied to Charmm36m, the simulated conductance significantly increases 7-fold, whereas applying ECC to Amber14 does not consistently increase the conductance. We further investigate this difference between ECC-Charmm36m versus ECC-Amber14sb by looking into the equilibrate distribution of the selectivity filter state using Hamiltonian Replica Exchange (HRE). We propose and test new parameters for Amber14sb that also predict a conductance similar to that of experiments and predict the I-V curve qualitatively close to the experiment for different potassium channels. Our modifications for both force fields reconcile Molecular Dynamics (MD) simulations and experimental data, in terms of ion occupancy in the selectivity filter, conductance, and current-voltage response, but not selectivity. In the channels (NaK2K, TRAAK, and MthK) with 2 force fields (Amber14sb and Charmm36m) tested in this study, no water co-permeation was observed. Overall, these refinements represent meaningful progress in the development of force fields for simulations of ion channels.

oral #375   **on-site**

Bayesian Electron Density Determination from Single-Molecule X-ray Scattering

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Co-author/s: Helmut Grubmüller

Single molecule X-ray scattering experiments using free electron lasers hold the potential to resolve both single structures and structural ensembles of biomolecules. However, structure refinement is exceedingly challenging due to complications such as low photon counts, high noise levels and low hit rates.
Most analysis approaches focus on large specimen like entire viruses, which scatter substantially more photons per image, such that it becomes possible to determine the molecular orientation for each image. In contrast, for small specimen like typical proteins the molecular orientation cannot be determined for each image, and must be considered random and unknown. Here we developed and tested a rigorous Bayesian approach for electron density determination from single-molecule X-ray scattering images, taking into account experimental effects such as hits and misses, intensity fluctuations, beam polarization, irregular detector shapes, incoherent scattering and background scattering. We demonstrate using synthetic scattering images that it should be possible to determine electron densities of small proteins in this extreme low hit-rate high noise Poisson regime. Notably, our results show that determining which of the millions of images are hits as opposed to misses, which becomes impossible for small molecules, is not required.

Oral #378   **on-site**

Molecular Mechanisms Unveiling Virus-Host Interactions Steering Membrane Fusion

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Viral infection relies on the stable binding of viral fusion proteins to host membranes, which comprise numerous lipid species. The process by which viruses sense lipid compositions to target suitable host cells, and how viral protein-lipid interactions propel membrane fusion, remains poorly understood. Through multi-scale molecular simulations, we calculated membrane binding free energies of fusion proteins spanning classes I–III, considering various lipid compositions. Our findings reveal membrane binding affinities follow the order: class I > class II > class III. This disparity in affinities implies different mechanisms followed by fusion proteins during membrane fusion. Class II and III proteins drive membrane fusion by specifically bind to polyunsaturated lipids at designated lipid binding pockets, aligning with their respective membrane fusion pathways. To assess the biological relevance of selective binding to polyunsaturated lipids, we conducted membrane fusion simulations. The stalks formed during membrane fusion exhibited an enrichment of polyunsaturated lipids, indicating that fusion proteins binding to such lipids prime the membrane for the initial stage of fusion through stalk formation. Considering the non-specific binding of lipids by class I proteins, we delved into the role of fusion peptides employed by class I to target the host membrane. Membrane-fusion simulations unveiled that fusion peptides from class I significantly reduce the free energy required to form stable stalks. Thus, beyond serving as host-membrane anchors, fusion peptides actively drive membrane fusion. Our results underscore the significance of lipid recognition by class II and III fusion proteins as a key feature for selective binding and fusing at the mammalian plasma membranes or membranes within endosomal compartments. Class I fusion protein which lack lipid binding pockets, utilize fusion peptides to anchor and drive membrane fusion.

oral #397   **on-site**

Microscopic Dynamics of an Intrinsically Disordered Protein in a Condensate

Presenting author: **Saumyak Mukherjee**

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Biomolecular condensates play a significant role in cell compartmentalization, allowing the organization of biochemical processes. The crowded environment of a condensate is characterized by a plethora of molecular interactions that determine its dynamical nature. Using atomistic molecular dynamics simulations, we aim to understand these interactions and decipher their effects on the internal dynamics of a FUS-LCD (Fused in Sarcoma Low Complexity Domain) protein condensate. We aim to understand the time- and length-scales of protein motions. Moreover, we determine the population and residence times of different dynamic amino acid contacts present in the condensate.

oral #401   **on-site**

Charges and Boundary Terms: Easy Ways to Spoil Your QM/MM(MD) Results

Presenting author: **Aleksandr Zlobin**

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Co-author/s: Phillipp Kachkin, Julia Beliaeva, Andrey Golovin

Hybrid quantum mechanical/molecular mechanical (QM/MM) simulations are a staple of modern computational biochemistry. A small portion of the molecular system is modeled with a more accurate QM approach, while keeping everything else under the much computationally cheaper MM description. This allows us to model enzymatic reactions in practice. To saturate open valencies on QM atoms when the subsystem is passed to the QM engine, capping hydrogen atoms are added. These atoms are called link atoms (LA) and are invisible to the MM engine. For QM engine, a LA placed along a bond to a sizably charged MM atom will be heavily influenced by it. This is called hyperpolarization, and it results in a setup that does not bear much chemical sense. A number of elaborate schemes to correct the issue were proposed. However, they have got limited traction in popular QM/MM software and, therefore, practice.

In biomolecular setting, two out of three backbone atoms are polar, and in QM/MM with electrostatic embedding, a neighboring intra-backbone link atom will be hyperpolarized. Here, we show that the consequences of such an artifact may be severe and may completely overturn the conclusions drawn from the simulations. Since QM/MM MD is getting ever more popular, we then investigated how different boundary types and charge redistribution schemes influence backbone dynamics. We showed that the results are heavily dependent on which boundary MM terms are retained, with charge alteration being of secondary importance. Only three intra-backbone boundaries produce correct results in dynamics when the classical scheme to omit angular and dihedral terms with only one MM atom is used. When these terms are retained, as implemented in Amber and NAMD suites, five out of six boundaries are mostly correct.

Our newest and unpublished results investigate the effects of both classical and Amber boundary term retainment schemes on the sidechain dynamics. We report that, quite worryingly, both schemes significantly alter chi-1 and chi-2 rotations. We then propose an updated term retainment scheme that alleviates this issue. Given the popularity of sidechain-only QM systems in practice, our results are of the utmost importance to all QM/MM MD practitioners.

oral #411   **on-site**

Proton Coupled Electron Transfer in Biomimetic Peptides

Presenting author: **Katharina Spies**

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Co-author/s: Marcus Elstner, Natacha Gillet, Tomas Kubar

Proton Coupled Electron Transfer (PCET) plays an important role in several biological processes involving the oxidation and reduction of aromatic residues such as tyrosine and tryptophan. Electron transfer is mediated along long-range transfer pathways involving a series of proton and electron transfer reactions. Insight into the environment that influences the mechanism of the PCET and the study of the structure and function of the tyrosyl radical and the adjacent residues are important for understanding the enzymatic reactions. Since experimental and computational studies of complex protein systems in which PCET plays an important role, such as photosystem II (PSII) and ribonucleic reductase (RNR), are costly, time-consuming and difficult to manage, biomimetic peptides and proteins are used instead. Theoretical studies can be essential for a deeper understanding of the reaction mechanism and the use of multiscale simulations is crucial: Molecular force-field methods correctly capture the protein environment that influences the donor and acceptor molecules involved in the transfer mechanism. Meanwhile, quantum chemistry accurately describes the particle motions, providing a comprehensive picture of these complex reactions.

The free energy surface of the reaction was obtained by tracking two collective variables along the simulation: 1) the proton tranfer as the difference of the distance between the donor and acceptor atoms to the transferred proton and 2) the electron transfer as the difference of the summed Mulliken charges. Two-dimensional multi walker metadynamic simulations were performed with biasing potentials applied to both CVs. For the later, the bias on the atomic charges, coupled-perturbed equations were implemented in the density functional tight binding (DFTB) method.

The methodology was tested on two types of biomimetic peptides. For the PSII-inspired β-hairpin peptides, the mechanism of the PCET reaction between a tyrosyl radical and either a histidine, tryptophan or tyrosine residue was investigated. It was found that the geometry, in which the residues are arranged relative to each other strongly influences the electron transfer. In addition, a α-helical radical maquette was studied and we were able to show the influence of the protein and water environment on the transfer mechanism.

oral #464   **on-site**

Investigation of Effect of Loop Motion on the Residence Time of Histamine-1-Receptor (H1R) Antagonists by τRAMD

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Co-author/s: Melanie Käser, Giulia D'Arrigo, Pierre Matricon, Chris de Graaf Rebecca C. Wade

Binding kinetics parameters, i.e. dissociation and association rate constants, can be more relevant than binding affinity as predictors of drug efficacy in non-equilibrium in vivo conditions. Therefore, a growing interest is emerging to develop methods to compute the drug-target dissociation rate constant or its inverse – residence time (τ). However, computing residence time is challenging due to dissociation occurring over a wide range of timescales (minutes and hours) – generally extending beyond timescales accessible by conventional molecular dynamics (MD) simulations. τRAMD is a method based on MD and enhanced sampling by Random Acceleration Molecular Dynamics (RAMD) for computing the relative residence times of ligand-protein complexes. In this study, τRAMD was applied to a set of compounds targeting Histamine-1-receptor (H1R). This protein is a member of the G protein-coupled receptors (GPCR) superfamily and is a validated target for the treatment of allergies and some forms of gastric acid related conditions. For some protein-ligand complexes, including H1R complexes, residence time is affected by the relatively slow motion of flexible loops. We modified the τRAMD protocol to account for the motion of a flexible loop and used it to compute the relative residence times of a set of antagonists of H1R. We find that the modified τRAMD protocol gives a better correlation of the computed residence times of the H1R antagonists with experimental values when compared to the standard τRAMD protocol. The τRAMD calculations also provide mechanistic insights into the H1R-ligand dissociation kinetics.

oral #482   **on-site**

Introducing the Automated Ligand Searcher

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The Automated Ligand Searcher (ALISE) is designed as an automated computational drug discovery tool. To approximate the binding free energy of ligands to a receptor, ALISE includes a three-stage workflow, with each stage involving an increasingly sophisticated computational method: molecular docking, molecular dynamics, and free energy perturbation, respectively. To narrow the number of potential ligands, poorly performing ligands are gradually segregated out. The performance and usability of ALISE are benchmarked for a case study containing known active ligands and decoys for the HIV protease. The example illustrates that ALISE filters the decoys successfully and demonstrates that the automation, comprehensiveness, and user-friendliness of the software make it a valuable tool for improved and faster drug development workflows.

oral #506   **on-site**

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

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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. 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. However, the mechanistic mode of action of lugdunin on membranes is hardly understood. Here, we applied atomistic molecular dynamics simulations to investigate lugdunin's differential interaction with a range of complex model membranes.
Our results suggest that lugdunin easily penetrates the membrane interface region, and is able to advance further into the membrane core. We decipher the driving forces behind lugdunin membrane embedment and in particular the role of the thiazolidine moiety. Microsecond-long simulations reveal the self-assembly of lugdunin molecules to stacks that span the membrane and form a channel likely capable of transporting protons. The presented simulations provide a basis for the future rational design of new macrocyclic thiazolidine peptide antibiotics with enhanced efficacy and safety profiles.

oral #529   **on-site**

Allosteric Communication in PDZ3 Studied by Nonequilibrium Simulations and Markov State Model

Presenting author: Ahmed Ali

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

While allostery is paramount for protein signaling and regulation, the underlying dynamic process of allosteric communication is poorly understood. PDZ3 domain represents a prime example of an allosteric single-domain protein, as it features a well-established long-range coupling between the C-terminal α3-helix and ligand binding. In an intriguing experiment, Hamm and coworkers [J. Phys. Chem. Lett. 2021,12,4262–4267] employed photoswitching of the α3-helix to initiate a conformational change of PDZ3 that propagates from the C-terminus to the bound ligand within 200 ns. Performing extensive nonequilibrium molecular dynamics simulations [J. Phys. Chem. Lett. 2022, 13, 9862–9868.] combined with Markov modeling, the modeling of the experiment reproduces the measured timescales and reveals a detailed picture of the allosteric communication in PDZ3. In particular, a correlation analysis identifies a network of contacts connecting the α3-helix and the core of the protein, which move in a concerted manner. Representing a one-step process involving direct α3-ligand contacts, this cooperative transition is considered an elementary step in the propagation of conformational change.

oral #541   **on-site**

Rest Assured: Programmed Translational Stalling Studied by Means of MD Simulations

Presenting author: Sara Gabrielli

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Co-author/s: Sara Gabrielli, Lars V. Bock

One way gene regulation occurs in bacteria is through programmed translational stalling. Specific arrest peptides have evolved to pause the ribosome under certain conditions while being translated. Thhe SecM arrest peptide, e.g. up-regulates secretion of proteins through the cell membrane by inducing stalling. A mechanical pulling force acting on the N-terminus terminates stalling and enables translation to continue. Recently, novel arrest peptides like ApdP have been discovered which share with SecM a conserved Arg-Ala-Pro-Pro motif. Cryo-EM structures of the stalled E. coli ribosome containing the peptide-Arg-Ala-Pro-tRNA in the ribosomal P site and a Pro-tRNA in the A site, suggest that peptide bond formation is affected during translation of ApdP and SecM.

In all current models of peptide bond formation, the nucleophilic attack of the aminoacyl-tRNA α-amino group to the carbonyl-carbon of the peptidyl-tRNA is facilitated by the extraction of a proton from the attacking α-amino group.

Using molecular dynamics (MD) simulations of the E. coli ribosome in complex with wt ApdP and non-stalling variants, we determined the protonation state of the A-site Pro and found that specific hydrogen bonds between the Arg-Ala-Pro peptide and the A-site Pro prevent the efficient adoption of conformations that allow the proton extraction as well as the subsequent nucleophilic attack required for peptide bond formation.

Additionally, we investigated, via unbiased and pulling simulations, how pulling of the N-terminus of SecM relieves stalling, identifying the sequence of events that leads to the disruption of the stalling conformation of the Arg-Ala-Pro-Pro motif.

oral #564   **on-site**

Absolute Binding Free Energy Calculations: A Systematic Force Field Comparison by a Newly Designed Computational Pipeline

Presenting author: **Alejandro Martínez-León**

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Co-author/s: Jochen S. Hub

Absolute binding free energy (ABFE) calculations based on free energy perturbation (FEP) techniques have emerged as a useful tool for guiding drug design. Although accuracy of ABFE calculations relative to experiment critically depends on the quality of the force field, systematic force field comparisons are still rare in the literature. To close this gap, we devised a computational pipeline "BindFlow" for fully auto-mated ABFE calculations. We computed ABFEs using the small-molecule force fields OpenFF-2.0.0, OpenFF-2.0.1, GAFF-2.11, and Espaloma-0.3.1. A total of 1239 affinities were computed, involving seven biological targets including a pentameric membrane channel. By computing uncertainties from three independent replicas for each ABFE calculation, we find that common methods such as MBAR underestimate the statistical uncertainties. Our results reveal marked differences among the force fields, both in terms of mean unsigned error relative to experiment and in terms of binding contributions from Lennard-Jones or Coulomb terms. Remaining challenges and future improvements are discussed.

oral #573   **on-site**

Molecular Modeling of the SARS-CoV-2 Nucleocapsid Protein Using Martini

Presenting author: **Balázs Fábián**

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Co-author/s: Stefan Sadowski, Jan Stuke, Gerhard Hummer

Biomolecular condensates have emerged as a novel mode of cellular organization that enables spatiotemporal control over complex biochemical reactions within the cell. Just as with many other physiological mechanisms, viruses also exploit condensates to ensure efficient viral replication and transmission. Among other functions, the abundantly expressed nucleocapsid (N) protein of SARS-CoV-2 forms the viral RNA—protein (vRNP) complex through liquid-liquid phase separation and organizes the packaging of these vRNPs into virions. Here, we investigate a Martini 3 model of the N protein by scaling protein-protein interactions to recapitulate the most prominent physicochemical properties of N protein condensates. Since the N protein has a pronounced net charge, we also systematically test different treatments of electrostatic interactions with respect to condensate properties. Using available structural and thermodynamic data we investigate the effect of phosphorylation on our model system and lay the foundations towards including RNA and M proteins in our model system. Additionally, we highlight some more general challenges of simulating biomolecular condensates at near-atomistic resolution.

oral #575   **on-site**

The Third Dimension of the Sugar Code under the Computational Microscope

Presenting author: Isabell Louise Grothaus

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Co-author/s: Giovanni Bussi, Carme Rovira, Jan-Hendrik Hehemann, Pauline Bolte

Glycans have an extremely important influence on all living matter on Earth. For instance, their occurrence in eukaryotic cells as post-translational modifications confers diverse functions to the underlying proteins. However, the so-called 'sugar code' that draws the connection between glycan structure and function still remains to be deciphered. Its unraveling is hampered by the vast amount of monosaccharide types, chemical substituents and linkages, resulting in a very large variety of glycan configurations. In addition, especially N-glycans are typically more flexible than proteins, a consequence of their many freely rotating torsion angles along the glycosidic bonds. The result is a large set of multiple conformations that can be adopted by each single (N-)glycan, opening a 'third dimension' of the sugar code beyond primary sequence and molecular topology.

The question remains to which extent this third dimension is biologically relevant, and if there exist relationships between the sequence, the three dimensional structure, and the function of (N-)glycans in their various biological environments. Computational techniques such as Molecular Dynamics (MD) simulations can be utilized to construct molecular glyco(protein) models and explore the many accessible glycan conformers in order to predict their function at the molecular level, a feature that very often cannot be covered by experimental techniques.

We therefore employ in-house-developed enhanced sampling MD methods like REST-RECT, combined with machine learning approaches and a new naming convention for glycans, to explore, represent and rationalise the conformational phase space of glycans in various biological environments.

The newly developed workflow allows us to:

1. unravel influences of N-glycans' conformations on important virulence factors like trans-sialidase enzymes involved in the sleeping sickness, Chagas disease and trypanosomiasis,

2. study the binding mode of N-glycans as substrates in the catalytic sides of CAZymes,

3. assess the structural riddle of marine polysaccharides that enable the storage of dissolved carbon in the deep sea, escaping bacterial degradation.

Each of these examples showed us that the third dimension of the sugar code is key in determining the properties and functions of carbohydrates in their various biological enviroments, broadening the view of what is yet to be uncovered in the field of glycobiology.

oral #584   **on-site**

High-Pressure Response of the Coupled Dynamics of Lipids and Membrane Proteins

Presenting author: Yanna Gautier

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Co-author/s: Guillaume Stirnemann, Jérôme Hénin

Cell membranes consist of a complex assembly of lipids and proteins that are essential to normal cellular function through their role as physical barrier, chemical filter or signal converter. The understanding of the interplay between the lipid properties, the collective physical properties of the membrane and the protein conformational landscape is key in order to explain the membrane protein function. Experimentally, high hydrostatic pressure can be used as a tool to modulate the lipids dynamics as well as a way to smoothly modulate the protein dynamics without denaturation. By combining high resolution liquid-state NMR and molecular dynamics (MD) simulation, we are characterizing the coupled dynamics of lipids and proteins in response to high pressures at the molecular level. We first demonstrate that state-of-the-art lipid forcefields enable to quantitatively reproduce the membrane phase transition at increasing pressure. As observed experimentally, the presence of a membrane protein such as OmpX shifts the phase transition to higher pressures. The MD simulations are then instrumental in providing a molecular picture of the protein's effect on the membrane lipids, in particular by providing a spatial resolution (that is, how lipids in contact with the protein are affected differently from those that are further away) that is not accessible in the experiments. In turn, we also characterize the lipid effect on the protein, and show that protein side-chains facing toward the membrane are very sensitive to the lipid phase transition, whereas groups pointing toward the protein core are much less affected, as suggested by the experimental results.

oral #609 **on-site**

Learning a State of the Art MM Force Field

Presenting author: Leif Seute

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Co-author/s: Eric Hartmann, Frauke Gräter

Simulating large molecular systems over long timescales requires force fields that are both accurate and efficient. While E(3) equivariant neural networks are providing a speedup over computational Quantum Mechanics (QM) at high accuracy, they are several orders of magnitude slower than Molecular Mechanics (MM) force fields.
Here, we present a state of the art machine-learned MM force field that outperforms traditional and other machine-learned MM force fields significantly in terms of accuracy, at the same computational cost. Our force field, Grappa, covers a broad range of chemical space: The same force field can parametrize small molecules, proteins, RNA and even uncommon molecules like radical peptides. Besides predicting energies and forces at greatly improved accuracy, Grappa is transferable to large molecules. We show that it keeps Ubiquitin stable and can fold small proteins in molecular dynamics simulations.
Grappa uses a deep graph attention network and a transformer with symmetry-preserving positional encoding to predict MM parameters from molecular graphs. The current model is trained on QM energies and forces of over 14,000 molecules and over 800,000 states, and is available for use with GROMACS and OpenMM.

oral #611   **on-site**

Evaporation Behavior of Common Water Models in Molecular Dynamics Simulations

Presenting author: **Patrick Quoika**

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Co-author/s: Martin Zacharias

Molecular Dynamics (MD) simulations are widely used to investigate molecular systems at atomic resolution including biomolecular structures, drug-receptor interactions and novel materials. Frequently, MD simulations are performed in aqueous solution with explicit models of water molecules. Commonly, such models are parameterized to reproduce the liquid phase of water at ambient conditions. However, often simulations at significantly higher temperatures are also of interest. Hence, it is important to investigate the equilibrium of the liquid and vapor phase of molecular models of water at various temperatures. We have evaluated the behavior of various rigid water models at various temperatures. From liquid-vapor coexistence simulations, we estimated the critical points and studied the spontaneous evaporation of these water models. Moreover, we investigated the influence of system size, choice of pressure-coupling algorithm and rate of heating on the process and compare it with experimental data. Interestingly, We found that the evaporation temperature and the critical temperature correlate with the quadrupole moment of the respective water model, which indicates that the spatial arrangement of the partial charges is a decisive parameter to reproduce the liquid-vapor phase transition. Our study may provide hints which water models may be used for simulations at elevated temperature.

oral #615   **on-site**

Understanding Errors in Relative Binding Free Energy Calculations

Presenting author: Sudarshan Behera

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Co-author/s: Vytautas Gapsys, David F. Hahn, Simone Marsili, Carter J. Wilson, Gary J. Tresadern, Bert de Groot

Alchemical free energy calculations have become increasingly robust, reliable and popular in drug discovery research. However, a comprehensive understanding and quantification of prediction errors (deviation from experiments) stemming from various assumptions[1] are crucial for the further advancement of the field. In this work, we systematically explored the error originating from the modelling of the initial structure in relative binding free energy (RBFE) calculations. We retrospectively analyze a large-scale dataset[2] of free energy simulations, followed by methodically altering the initial structure of the protein-ligand complex in several good-performing RBFE calculations (with error <= 1 kcal/mol). This was done by generating rotamers of ligand and amino acid side chains of the protein-ligand binding site. In addition, the dependence of prediction errors on the crystal structure of the protein-ligand complex (hence, the effect of placement of water and ligand in the binding site) was investigated by preparing a dataset with varied resolutions of crystal structure. In summary, we offer a thorough assessment and quantification of the predictive errors resulting from various aspects of the system set-up in large-scale RBFE simulations. Our study thus produces a base for developing rules, guidelines and improvements for future alchemical calculations.

[1] Hahn, David F., et al. "Current state of open source force fields in protein-ligand binding affinity predictions." (2023). https://doi.org/10.26434/chemrxiv-2023-ml7gd
[2] Gapsys, Vytautas, et al. "Large scale relative protein ligand binding affinities using non-equilibrium alchemy." Chemical Science 11 (2020): 1140-1152. https://doi.org/10.1039/C9SC03754C

oral #616   **on-site**

Delineating the Shape of COPII Coated Membrane Bud

Presenting author: Sanjoy Paul

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Co-author/s: Qiang Cui

Curvature generating proteins assemble on the membrane surface to bud vesicles for transporting protein cargoes from one cellular compartment to the other. Many of these proteins initiate the curvature induction by inserting their helical amphipathic regions where hydrophobic and hydrophilic residues are partitioned at the membrane water interface. Our latest research on the COPII molecular machinery protein Sar1 revealed that, regardless often addition to the protein's penetration depth, the ability to bend the membrane surface is controlled by the volume inclusion of the protein inside the membrane. However, after initiating the curvature induction, what determines the shape of the membrane bud remains an open question. In vitro experiments reveal that a high concentration of Sar1 results into in a tubular growth on the GUV whereas in vivo COPII coated vesicles are spherical in nature. It is important to note that Sar1 together with Sec23/24 form the inner coat assemblies where it is unknown whether Sec23/24 also contribute to the curvature induction. We hypothesize that Sec23/24 functions as a spacer to maintain an orderly Sar1 lattice modulate the distribution and orientation of Sar1 proteins and therefore , which keeps the shape of the membrane buds spherical form. We use the dynamical triangulated surface simulation approach to model the inner coat assembly, where the membrane is viewed as a surface-enclosed triangular mesh, and the Helfrich Hamiltonian governs its dynamics with non-zero intrinsic curvature at the protein containing mesh vertices. We reveal that the anisotropic protein membrane coupling leads to a disc like shape of the membrane bud while isotopic interactions give rise to a more spherical budding. Additionally, we dope some of the protein-containing regions with zero intrinsic curvature to represent Sec23/24 presence and its impact on membrane shape. Overall, our present analyses emphasize the importance of considering mapping between the orientations of a collection of amphipathic helices and the shape of the membrane bud.

COMPUTER SIMULATION AND THEORY OF MACROMOLECULES

Hünfeld, April 19-20, 2024, Hybrid

Section 2:

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Poster #91   **on-site**

Characterization of the Bottlenecks and Pathways for Inhibitor Dissociation from [NiFe] Hydrogenase

Presenting author: **Farzin Sohraby**

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Co-author/s: Ariane Nunes-Alves

Hydrogenases are important enzymes due to their ability to act as efficient catalysts for hydrogen oxidation and biofuel production. However, some NiFe hydrogenases are inhibited by O2 and CO. A possible strategy to obtain resistant enzymes is to block access to the catalytic site by engineering mutant forms. In this work, we characterized the unbinding pathways of CO in complex with the wild type and 10 different mutants of [NiFe] hydrogenase from Desulfovibrio fructosovorans using τ-Random Accelerated Molecular Dynamics (τRAMD) to enhance the sampling of unbinding events and find key features governing the access of gas molecules to the active center. The residence times computed with τRAMD are in agreement with the experimental ones. Extensive data analysis of the simulations revealed that, from the two bottlenecks proposed in previous studies for the transit of gas molecules (residues 74 and 122, and residues 74 and 476), only one of them (residues 74 and 122) effectively modulates diffusion and residence times for CO. We also computed pathway probabilities for the unbinding of different gas molecules from the wild type [NiFe] hydrogenase and we observed that, while the most probable pathways are the same, the secondary pathways are different. We propose that mutations to block the most probable paths, in combination with mutations to open the main secondary path used by H2, can be a feasible strategy to achieve CO and O2 resistance in the [NiFe] hydrogenase from Desulfovibrio fructosovorans.

Poster #93   **on-site**

Modelling Contrast-Variation SAXS Experiments by Explicit-Solvent Molecular Dynamics

Presenting author: Noora Aho

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Co-author/s: Jochen S. Hub

Small angle X-ray scattering (SAXS) has established its role in structural biology during the last decades, providing information on the shape, interactions and large-scale conformational transitions of biomolecules in solution. In addition, so called contrast-variation SAXS, where the scattering data is recorder at multiple solvent electron densities, adds the possibility to measure electron densities of biomolecular assemblies enabling the visualisation of distinct biomolecules [1]. The interpretation of experimental SAXS data requires the accurate calculation of SAXS curves from structural models. To achieve this, explicit-solvent molecular dynamics (MD) is a powerful method, taking into account both the atomistic accuracy and correct thermal fluctuations in the scattering curve calculations [2]. In this work, our aim is to expand the application of explicit-solvent MD simulations from conventional SAXS to contrast-variation SAXS experiments. We model the ferrichrome membrane transporter protein FhuA in the presence of lanthanide contrast agents in explicit solvent and calculate corresponding SAXS curves using MD simulations. In addition to supplementing experimental SAXS data for the specific protein, our simulations serve as an example of the possibilities of explicit-solvent MD in interpretation of advanced SAXS experiments.

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Poster #104   **on-site**

A Double Mutation in the Pore of the Large Conductance Mechanosensitive Channel Helps to Unravel the Mechanism of its Gating

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The Large Conductance Mechanosensitive Ion Channel (MscL) is a bacterial protein 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 MscL opening. While X-Ray structure of the MscL in the closed state is available in PDB, experiments encounter difficulties in determining the open state structure. Moreover, the high tension activation threshold makes simulation of the wild-type MscL quite challenging. To overcome these difficulties, we applied an unbiased molecular dynamics approach to the MscL double mutant (L17A, V21A). This mutant destabilizes the closed state of MscL and thereby promotes channel opening.
We simulated the MscL mutant at a constant surface tension of 30 mN/m using a Berendsen pressure coupling. Under these conditions, it takes about a microsecond for the mutant to spontaneously undergo a transition from the closed state to the state we call "expanded." The "expanded" state has many features in common with the putative open state, such as conductance and a set of distance restraints, but it cannot be considered an open state because it does not satisfy all the distance restraints known from experiments. Most likely, the transition from the closed to the "expanded" state does not simultaneously affect the five MscL chains, but rather the chains move one after another, resulting in a series of fast local transitions. We estimated free energy profiles of these local transition and proposed collective variables that may be effective in accelerating the wild-type MscL transition.

Poster #159   **on-site**

Amyloid-β Oligomer Conformations and Membrane Permeabilization

Presenting author: Dirk Matthes

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Co-author/s: Bert de Groot

Oligomeric aggregates of the amyloid-beta peptide(1-42) (Aβ42) are regarded as a primary cause of cytotoxicity related to membrane damage in Alzheimer's disease. However, a dynamical and structural characterization of pore-forming Aβ42 oligomers at atomic detail has not been feasible. Here, we used Aβ42 oligomer structures previously determined in a membrane-mimicking environment as putative model systems to study the pore formation process in phospholipid bilayers with all-atom molecular dynamics simulations. Multiple Aβ42 oligomer sizes, conformations, and N-terminally truncated isoforms were investigated on the multi-μs time scale. We found that pore formation and ion permeation occur via edge conductivity and exclusively for β-sandwich structures that feature exposed side-by-side β-strand pairs formed by residues 9 to 21 of Aβ42. The extent of pore formation and ion permeation depends on the insertion depth of hydrophilic residues 13 to 16 (HHQK domain) and thus on subtle differences in the overall stability, orientation, and conformation of the aggregates in the membrane. Additionally, we determined that backbone carbonyl and polar side-chain atoms from the edge strands directly contribute to the coordination sphere of the permeating ions. Our findings suggest that membrane-inserted, layered β-sheet edges are a key structural motif in pore-forming Aβ42 oligomers independent of their size and play a pivotal role in aggregate-induced membrane permeabilization.

Poster #162 **on-site**

Do Coarse-grained Simulations capture the Free Energy Landscape of Membrane Topological Transitions?

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Co-author/s: Joel Chavarria Rivera, Leonhard Starke, Jochen S. Hub

Biological membranes undergo significant topological transitions during essential processes like membrane fusion or pore formation. These transitions lead to the reshaping of membranes into non-bilayer conformations. While the general rearrangements of membranes are known, capturing the free energy landscape of these topological transitions remains a substantial challenge. We use MD simulations to calculate the potential of mean force along a reaction coordinate, serving as a measure of connectivity between two compartments. This computationally efficient approach allows us to explore the energetics associated with membrane fusion and pore formation and expansion, not only at coarse-grained level but also with atomistic resolution. We discuss remarkable agreement between atomistic and coarse-grained resolution, while also addressing and explaining crucial discrepancies between the two. Our findings systematically elucidate the scenarios in which a coarse-grained force field accurately represents the free energy of membrane topological transitions.

Poster #163   **on-site**

H-Bond Network Analysis of Cytochrome C Oxidase

Presenting author: **Jesse Jones**

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Co-author/s: Maria Andrea Mroginski

Cytochrome c Oxidase is the terminal enzyme of the cell respiratory chain, catalyzing the reduction of O2 to H2O. Proton pumping across the membrane occurs coupled to the reduction. 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. Finally, the MDAnalysis suite is used to identify key hydrogen bonds.

Poster #170 **on-site**

Influence of Temperature and Surface Composition on the Protein Hydration Shell

Presenting author: Johanna-Barbara Linse

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Co-author/s: Hyun Sun Cho, Philip A. Anfinrud, Jochen S. Hub

The proteins hydration shell plays key roles in protein stability, folding, recognition, enzyme activity and several others. However, it remained unclear how strong the hydration shell around the protein is influenced by the temperature, as experimental data on hydration shell structures for different temperatures were limited. Small-angle X-ray scattering (SAXS) experiments provide insights into hydration shell properties, because the detected radius of gyration and zero-angle scattering depend on the hydration shell contrast relative to the bulk solvent. Using explicit-solvent MD simulations and SAXS calculations, we calculated the radius of gyration values for calmodulin, villin and the GB3 domain, using the TIP4P/2005 water model in combination with the amber99SB-ildn force field. Validation of the results against data from temperature jump SAXS experiments revealed remarkable agreement between MD simulations and experiments. Furthermore, we investigated the influence of amino acid surface composition of proteins on the hydration shell contrast, providing contrast scores for the 20 canonical amino acids. Our studies show that explicit-solvent SAS calculations and SAS data provide novel routes for predicting the amino acid and temperature effects on the hydration shell structure.

Poster #176   **on-site**

Analyzing the Free Energy Landscape of Aβ42 Conformational Switching

Presenting author: Moritz Schäffler

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Co-author/s: Birgit Strodel, David Wales

The amyloid-β peptide (Aβ) is an Intrinsically Disordered Protein (IDP) that is being studied intensively as it is strongly linked to the development of Alzheimer's disease. IDPs do not fold into a unique three-dimensional structure but sample a wide range of configurations that further change with the surrounding of the IDPs. The structural heterogeneity and dynamics of IDPs pose a challenge for the characterization of their structures by experimental techniques only. Molecular dynamics (MD) simulations are a powerful complement to experimental approaches for that purpose. Conformational Transition Networks (TNs) provide advanced capabilities for elucidating structural preferences of IDPs and the kinetics of conformational transitions.
Recently, we applied the TN approach to study conformation switching of the Aβ42 Monomer when in contact with a Glycosaminoglycan (GAGs). Additionally we studied the Free Energy Surface (FES) using disconnectivity graphs, which gives further insights into the dynamics and conformational switching of Aβ42.

Poster #196   online

Collagen Structured Hydration

Presenting author: Satyaranjan Biswal

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Co-author/s: Noam Agmon

Collagen is a triple-helical protein unique to the extracellular matrix, conferring rigidity and stability to tissues such as bone and tendon. For the [(PPG)10]3 collagen-mimetic peptide at room temperature, our molecular dynamics simulations show that these properties result in a remarkably ordered first hydration layer of water molecules hydrogen bonded to the backbone carbonyl (bb-CO) oxygen atoms. This originates from the following observations. The radius of gyration attests that the PPG triplets are organized along a straight line, so that all triplets (excepting the ends) are equivalent. The solvent-accessible surface area (SASA) for the bb-CO oxygens shows a repetitive regularity for every triplet. This leads to water occupancy of the bb-CO sites following a similar regularity. In the crystal-phase X-ray data, as well as in our 100 K simulations, we observe a 0-2-1 water occupancy in the P-P-G triplet. Surprisingly, a similar (0-1.7-1) regularity is maintained in the liquid phase, in spite of the sub-nsec water exchange rates, because the bb-CO sites rarely remain vacant. The manifested ordered first-shell water molecules are expected to produce a cylindrical electrostatic potential around the peptide, to be investigated in future work.

Poster #228   **online**

Can Azo Pyrimidine Work as Molecular Switch: A Computational Study

Presenting author: Shaaban Elroby

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Co-author/s: Saadullah G Aziz, Osman I Osman

Today, the development of new dyes and optical devices depends on the development of novel chromophores with distinct photophysical properties. Most commercial dyes are composed of azobenzene derivatives, which are still essential in the development of general-purpose photoactivated switches. To lay the groundwork for the long-term goal of developing dyes with particular photophysical properties, we have studied the optical and photoisomerization properties of two pyrimidine azo dye (PYAZ) from a purely theoretical perspective. This study provides a complete analysis of the electronic and photophysical properties of cis-trans isomerization of PYAZ. Density Functional Theory (DFT) and Time Dependent Density Functional Theory (TD-DFT) methods have been employed. All the geometrical structures in the singlet ground (S0) and excited (S1 and S2) states, were optimized using CAM-B3LYP/6-311+G** level of theory in the ground state and solution. Furthermore, the absorption and emission spectra were simulated using different density functionals (PBEPBE, CAM-B3LYP and BMK). PYAZ with an electron withdrawing group shows large stokes shift compared with those having electron-donating ones.

Poster #263   **on-site**

Large Scale Biomolecular Simulations in the Cloud

Presenting author: Carsten Kutzner

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Co-author/s: N Kozlowski, C Kniep, L Nordstrom, A Cherian, BL de Groot, V Gapsys, H Grubmüller

Alongside traditional providers of high-performance computing resources such as universities and supercomputing centres, the Cloud has emerged as an additional and competitive option for scientific computing. While it is frequently dismissed as too expensive, this is a common misconception. Moreover, the Cloud offers possibilities that are not present on traditional clusters. Looking back at several simulation projects that we have successfully run in the Cloud, we summarise our three years of experience with GROMACS simulations on Amazon Web Services (AWS). We show that Cloud-based simulations can be optimised to be as cost-effective as operating an on-premises compute cluster. In particular, when ensembles of thousands of independent simulations need to be run, we have had consistently good experience with an AWS Cyclone-based setup that allows us to take advantage of excess global compute capacity available at a deep discount on the Spot market. This gives us almost instant access to a few thousand GPU instances, so that even large simulation projects can be completed quickly.

Poster #278   **on-site**

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

Presenting author: Eliane Briand

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

The protonation state of residues plays a major role in the dynamics of proteins, therefore computational methods that allow for time-varying protonation state changes, like constant pH molecular dynamics (MD), are necessary for optimal simulation accuracy. Contributing to this goal, we present the latest additions to our constant pH MD implementation for the GROMACS MD package, using the GPU-accelerated Fast Multipole Method electrostatics. New applications and post-processing workflows are also demonstrated for the study of protonation dynamics in biomolecular systems.

Poster #305 **on-site**

Bayesian Structure Determination Approach for Single Molecule X-ray Scattering

Presenting author: Stefan Tessarini

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Co-author/s: Steffen Schultze, Helmut Grubmüller

Proteins control most processes in living cells, where their function is linked to the structure and often also to the dynamics between different structural configurations. Current state-of-the-art structure determination methods, despite their success, are suffering from averaging effects when multiple structural conformations are present in the sample. Single molecule X-ray scattering with free electron lasers has been shown to be a promising candidate for molecular structure determination. The method avoids averaging effects between different conformations and has the potential for determination of structure ensembles as well as imaging the dynamics of confrontational changes. The challenges posed by the unknown orientation and conformation of the protein and the weak scattering signal of typically only a few photons per image were solved using a Bayesian approach. This work continues the development of the Bayesian structure determination approach with the aim to incorporate prior information in the reconstruction process.

Poster #306   **on-site**

Developing Coarse Graining RNA Force Fields via Machine Learning

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Co-author/s: Alex Schug, Emile de Bruyn, Stefan Kesselheim, Fabrice von der Lehr, Philipp Knechtges

In Protein structure prediction there have been massive improvements recently due to deep learning driven exploration of the rich experimental data. A direct transfer, however, of these methods to RNA structure prediction is impossible due to much sparser experimental data for RNA. Still, the combination of molecular force fields with constraints derived from statistical analysis of genomic data such as direct coupling analysis can lead to good quality structure predictions also for RNA. Here, we want to optimize the accuracy of the employed coarse-grained RNA force field for the molecular simulations by employing machine learning techniques. The data sparsity can here be alleviated by building on established atomistic RNA force fields. In a first step we show the viability of this approach by focusing on small RNA molecules in Molecular Dynamics simulations. We explore different bead numbers for the coarse graining to determine the best approximation.

Poster #307   **online**

Peripheral linker mediates ACP's recognition of DH and stabilizes Mycobacterium tuberculosis FAS-I

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Incomplete structural details of Mycobacterium tuberculosis (Mtb) fatty acid synthase-I (FAS-I) at near-atomic resolution have limited our understanding of the shuttling mechanism of its mobile acyl carrier protein (ACP). Here, we have performed atomistic molecular dynamics simulation of Mtb FAS- I with a homology-modelled structure of ACP stalled at dehydratase (DH), and identified key residues that mediate anchoring of the recognition helix of ACP near DH. The observed distance between catalytic residues of ACP and DH agrees with that reported for fungal FAS-I. Further, the conformation of the peripheral linker is found to be crucial in stabilizing ACP near DH. Correlated inter-domain motion is observed between DH, enoyl reductase (ER) and malonyl/palmitoyl transferase (MPT); consistent with prior experimental reports of fungal and Mtb FAS-I.

Poster #317   **online**

Modulation of α-Synuclein Aggregation Amid Diverse Environmental Perturbation

Presenting author: Abdul Wasim

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The involvement of the intrinsically disordered protein α-Synuclein (αS) in Parkinson's disease is linked to its abnormal tendency to aggregate. To uncover the characteristics of its aggregation, we conducted computational simulations to explore the multi-chain association process of αS in both aqueous environments and various environmental conditions. The aggregation of αS in both aqueous and diverse environmental settings resulted in significant concentration variations within protein aggregates, resembling liquid-liquid phase separation (LLPS). The LLPS propensity was heightened in saline and crowded conditions. However, the response of the surface tension of αS droplets differed between crowders (entropy-driven) and salt (enthalpy-driven). Conformational analysis revealed that intrinsically disordered protein chains would assume extended conformations within aggregates, maintaining mutually perpendicular orientations to minimize inter-chain electrostatic repulsions. The stability of the droplets was attributed to reduced intra-chain interactions in the C-terminal regions of αS, promoting inter-chain residue-residue interactions. Notably, a graph theory analysis identified small-world-like networks within droplets across various environmental conditions, indicating a consensus in interaction patterns among the chains. These findings collectively suggest a delicate equilibrium between molecular grammar and environment-dependent nuanced aggregation behavior of αS.

Poster #320   **on-site**

TRAP Mediated Conformational Changes of the Sec61 Channel in Human

Presenting author: Nidhi Sorout

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Co-author/s: Nicolas Künzel, Volkhard Helms

The Sec61 translocon mediates the translocation of numerous freshly synthetized proteins either into the lumen of the endoplasmic reticulum or into its membrane. Some substrate peptides require the help of other auxiliary factors such as the presence of the heterotetrameric translocon-associated protein (TRAP) complex. The mechanism by which TRAP affects the Sec61 translocation is unknown. To investigate the effect of accessory protein TRAP on the conformational dynamics of the Sec61 channel, we performed multiple atomistic molecular dynamics simulations started from the cryo-EM structure of Sec61 bound to TRAP and of Sec61 alone, embedded in a lipid bilayer. We have observed the conformational transitions near the lateral gate and of the plug in the unbound Sec61 relative to the TRAP-bound Sec61 channel. The diagonal distances that describe the channel pore were also affected by the presence/absence of TRAP. Thus, our study explains the effect of TRAP on the conformational transition of Sec61.

Poster #332   **on-site**

Quantifying Membrane Perturbation Induced by Membrane-Remodeling Proteins

Presenting author: Kateryna Lohachova

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Co-author/s: Sergio Alejandro Poveda-Cuevas, Arghya Dutta, Ramachandra M. Bhaskara

Large-scale protein-induced membrane remodeling events are central to organellar and cellular homeostatic pathways. The interplay of membrane proteins (integral and peripheral) and lipids controls their intrinsic curvature fields and emergent properties. Despite advances in experimental and theoretical approaches, the quantification of protein-induced membrane perturbations has remained elusive. Here, we use large-scale coarse-grained MD simulations on several families of membrane remodeling factors in model bilayers to precisely quantify their intrinsic curvature fields, decoupling them from boundary effects. Here, we model protein molecules as membrane inclusions with distance-dependent anisotropic spontaneous fields to exploit the Helfrich elastic theory and apply it to particle-based simulations. By minimizing the Helfrich bending energy of protein-containing membrane patches and their varied local geometries sampled during MD simulations, we quantify protein-specific curvature fields representative of the key membrane-shaping elements found in remodeling factors. Protein-specific parameters obtained here can be readily assimilated into continuum and triangulated models, thereby bridging the molecular and mesoscale. Our findings provide accurate computational models of membrane remodeling proteins, providing direct quantification of their membrane perturbations and insights into the general principles of protein-induced membrane curvature, with potential applications for the rational design of drugs to modulate membrane remodeling processes.

Poster #354   **on-site**

Simulation of Lipid Membranes and Their Interaction with Polystyrene

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Co-author/s: Thorsten Koslowski

Outstanding properties and a wide range of applications make polystyrene one of the most widely used plastics in the world. Consequently, more and more polystyrene nanoparticles are contaminating nature and biological organisms. This gives rise to the question how styrene polymers or oligomers interact with, f.ex., cells or lipid membranes.
In this work we investigated the interactions of a styrene molecule and styrene oligomers with a lipid membrane by calculating the free energy differences. The system was simulated using the umbrella sampling method to overcome energy barriers. This method uses a harmonic bias potential along the reaction coordinate to provide the potential of mean force (PMF).
For completeness, we also calculated the free energy difference of decoupling a styrene molecule from water or bulk, via thermodynamic integration.
Combining both results gives an overview of the energetical landscape of the molecule inside and outside of the lipid bilayer; it also enables the formulation of a theoretical model to describe the interactions between the particles.

Poster #355   **on-site**

NrfH in External Electric Fields: Protonation and Dielectrics

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Co-author/s: Jetmir Haxhija, Mike Castellano, Thorsten Koslowski

The study of the interaction between external electric fields and biological molecules has attracted increasing attention because of its potential implications for understanding and manipulating cellular processes [1,2]. The present study focuses on investigating the response of NrfH, a key participant in cellular homeostasis and redox regulation, to external electric fields. Specifically, the effect of these fields on the pKa of amino acids in NrfH was investigated using molecular dynamics simulations. The results obtained indicate that electric fields induce changes in the protonation patterns of selected amino acids. Subsequently, the proton-electron interactions in NrfH was then carried out using continuum dielectric theory, which revealed a small electron-proton interaction in NrfH. Furthermore, the voltage distribution along NrfH was computed using the numerical solution of the Laplace equation. After studying various parameters such as system geometry, humidity and membrane thickness, it was found that the primary voltage drop occurs within the membrane.

This study provides valuable insights into the molecular mechanisms underlying the response of NrfH to external electric fields. In addition, our findings contribute to a broader understanding of the electrostatic modulation of biological macromolecules, thereby providing the basis for future research efforts in the fields of bioelectricity, medicine and biotechnology.

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Poster #367   **on-site**

Understanding the Redshift in the Absorption Spectrum of the FAD cofactor in ClCry4 Protein

Presenting author: **Katarina Kretschmer**

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

It is still a puzzle how some migratory birds utilize the Earth's magnetic field for biannual migration. The most consistent explanation so far roots on modulation of the biological function of the Cryptochrome 4 (Cry4) protein by external magnetic field. This phenomenon is closely linked with the FAD cofactor that is bound in the protein. The Cry4 protein with the bound FAD cofactor is activated by blue light, absorbed by the FAD cofactor. Through several transfers that trigger radical pair formation in Cry4, the protein can become sensitive to the geomagnetic field. An important redox state of the FAD cofactor is the signaling state, which is present after completion of the different electron transfers inside the protein. Recently it has been possible to crystallize the Cry4 protein from Columbia Livia (ClCry4) with the associated important residues needed for photoreduction. It is the most promising crystallization of the Cry4 protein so far, which also has great similarity with the Cry4 proteins of night migratory birds. The absorption spectrum of the FAD cofactor inside the ClCry4 protein was investigated experimentally in its different redox states during protein's activation. The absorption spectrum of the signaling state demonstrated a redshift if compared to the photoabsorption properties of the FAD cofactor in its signaling state in other Cry proteins. The aim of this study is to understand this redshift by employing the tools of computational microscopy, and in particular the QM/MM approach.

Poster #368   **on-site**

A Realistic Outer Membrane Model of the Bacterium Escherichia Coli

Presenting author: Charalampos Ntallis

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The rapid emergence of Gram-negative 'superbugs' adds significantly to the antimicrobial resistance (AMR) crisis and has an overwhelming impact on human health worldwide. The development of next-generation drugs that can overcome AMR requires the understanding of the atomic scale structural details that explain the killing mechanisms. Gram-negative bacteria possess unique characteristics related to the cell envelope which make it a daunting task to design novel drugs against them.
The cell envelope of Gram-negative bacteria consists of an inner membrane (IM), a thin peptidoglycan (PG) cell wall and an outer membrane (OM), with the latter being the target of lipopeptide antibiotics of last resort for treating multi-drug resistant infections (e.g., polymyxins). The OM is a unique asymmetric bilayer and the complex lipopolysaccharides (LPS) render its structure and dynamics still poorly understood.
In this study, we present a computational approach to build a realistic and asymmetric OM model of the Gram-negative bacterium Escherichia coli (E. coli) using all-atom molecular dynamics simulations and high-performance computing. Resistant E. coli strains are frequently associated with extra-intestinal human infections, e.g., bloodstream or urinary tract infections. This model will serve for the understanding of the killing mechanism of antibiotics that target the OM, through the integration of solid-state NMR and computational chemistry approaches. Highlighting the molecular mechanisms that lead to AMR in pathogenic Gram-negative
bacteria can provide the rational for designing new therapeutic strategies.

Poster #370   **on-site**

Data-driven Identification and Analysis of the Glass Transition in Polymer Melts

Presenting author: **Atreyee Banerjee**

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On cooling, the dynamical properties of many polymer melts slow down exponentially, leading to a glassy state without any drastic change in static structure. Understanding the nature of glass transition, as well as precise estimation of the glass transition temperature (Tg) for polymeric materials, remain open questions in both experimental and theoretical polymer sciences. We propose a data-driven approach, which utilizes the high-resolution details accessible through the molecular dynamics simulation and considers the structural information of individual chains. It identifies the glass transition temperature of polymer melts of semiflexible chains. By combining principal component analysis (PCA) and clustering, we identify glass transition temperature at the asymptotic limit even from relatively short-time trajectories, which just reach into the Rouse-like monomer displacement regime. We demonstrate that fluctuations captured by the principal component analysis reflect the change in a chain's behaviour: from conformational rearrangement above to small vibrations below the glass transition temperature. We demonstrate the generality of the approach by using different dimensionality reduction and clustering approaches. The method can be applied to a wide range of systems with microscopic/atomistic information. More recently we applied this methodology to all-atom acrylic paint systems. Our study reveals the explicit role of backbone and side chain residues in determining the glass transition temperature.

Poster #376 on-site

Regulation of Substrate Transport in the Early Stages of Fatty Acid Synthesis

Presenting author: Florian Leidner

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Co-author/s: Helmut Grubmüller

The fungal type 1 fatty acid synthase (FAS) is a complex multienzyme system that plays a crucial role in the synthesis of saturated fatty acids. The progression of the intricate reaction cycle relies on the transfer of reaction intermediates between catalytic domains, facilitated by an acyl carrier domain. The initial step of the reaction involves the transfer of acetyl to the carrier, necessitating a substantial conformational change that is stabilized by the binding of a regulatory γ-subunit. This study aims to elucidate the molecular mechanism underlying the induction of the conformational change and the stabilization of the initiation complex. To achieve this, all-atom molecular dynamics simulations were performed on the FAS in the initiation conformation. A comprehensive model of the full-length 2.6 MDa FAS complex was reconstructed, serving as the basis for the simulations conducted in the presence and absence of the γ-subunit, as well as by relocating the carrier to different catalytic domains. The results demonstrate that the binding of the γ-subunit is essential for stabilizing the conformational change, whereas the binding of the carrier protein did not exert a significant effect. These findings support the hypothesis that the initiation of fatty acid synthesis is regulated through conformational selection, rather than solely relying on the binding and dynamics of the carrier protein.

Poster #383   **online**

Switching Gō-Martini for Investigating Protein Conformational Transitions and Associated Protein-Lipid Interactions

Presenting author: Song Yang

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Proteins are dynamic biomolecules that can transform between different conformational states when exerting physiological functions, which is difficult to simulate by using all-atom methods. Coarse-grained Gō-like models are widely-used to investigate large-scale conformational transitions, which usually adopt implicit solvent models and therefore cannot explicitly capture the interaction between proteins and surrounding molecules, such as water and lipid molecules. Here, we present a new method, named Switching Gō-Martini, to simulate large-scale protein conformational transitions between different states, based on the switching Gō method and the coarse-grained Martini 3 force field. The method is straightforward and efficient, as demonstrated by the benchmarking applications for multiple protein systems, including glutamine binding protein (GlnBP), adenylate kinase (AdK), and β2-adrenergic receptor (β2AR). Moreover, by employing the Switching Gō-Martini method, we can not only unveil the conformational transition from the E2Pi-PL state to E1 state of the Type 4 P-type ATPase (P4-ATPase) flippase ATP8A1-CDC50, but also provide insights into the intricate details of lipid transport.

Poster #385   **on-site**

Maximum Entropy Ensemble Refinement for NOEs

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Co-author/s: Bert de Groot, Michael Habeck, Daniel Rudolf

In some cases, features experimentally measured from a protein ensemble, like atom distances, are not recovered on average in molecular dynamics simulations. 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, in order to fulfil all measured data. The problem then presents as a doubly intractable Bayesian inference problem and thus requires sophisticated two-step Monte Carlo methods. We focus on NOE measurements, where the measured peak intensities are proportional to the inverse sixth power of atomic distance. Ensembles derived using the corresponding maximum entropy energy terms in a modified molecular dynamics simulation show a wider variety of structures than ensembles derived by other refinement methods while still satisfying measured feature bounds on average.

Poster #393   **on-site**

Elucidating the Exciton Transfer Mechanism in LHCII Through ML

Presenting author: Ebru Akkus

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Co-author/s: Marcus Elstner

A deep understanding of the exciton transfer mechanism in the major antenna trimer Light Harvesting Complex II (LHCII) is necessary to comprehend the complex mechanism of photosynthesis in plants. For this, we will simulate LHCII classically and perform DFTB+ calculations to get crucial informations on the exciton transfer via the system's Hamiltonian which includes excitation energies (site energies) and interactions between chlorophylls (couplings) through the extensive trajectories. To obtain the exciton transfer dynamics, machine learning (ML) techniques will be utilized to speed up the most costly part of the study.

Poster #406   **on-site**

Unraveling the Structure of Self-Assembled Cyanine Dye Nanotubes

Presenting author: Ilias Patmanidis

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Cyanine dyes are a family of molecules whose members are known to aggregate and form different types of supra-molecular structures with discrete features. One of the cyanine dyes that has been extensively studied the past decades is 1,1'-dioctyl-3,3'-bis(2-sulfopropyl)-5,5',6,6'-tetrachloro-benzimida-carbocyanine (C8S3), which self-assembles into double-walled nanotubes. The C8S3 nanotubes present structural similarities with light-harvesting antennae found in green sulphur bacteria, and they exhibit fast and efficient energy transfer. Understanding their structural and functional features will allow us to design similar molecules with tuned properties for applications in labelling, light harvesting complexes, optical switches, etc. We employed a combination of molecular dynamics simulations at different resolution (all atom and coarse grained), theoretical modelling and experimental techniques to shed light on the structure and optical features of C8S3 nanotubes. Our results provide answers on the dimensions of C8S3 nanotubes at high resolution, the molecular packing of the dyes inside the nanotubes and the effect of disorder at stages of their self-assembly process.

Poster #407   **on-site**

Using Alchemical Free Energy Simulations for Protein Design

Presenting author: Lisa Schmidt

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Co-author/s: Bert de Groot

Protein Structure-Switches are important in many biological processes and exhibit great structural diversity. This makes them interesting targets for protein design studies with the aim to make programmable proteins. Even though protein design has made remarkable progress in the last years, designing controllable structure switching proteins is still a challenging task.

We apply Alchemical Free Energy simulations with PMX to calculate the mutation free energy differences between different protein conformations. We focus on three different proteins with different structure switching behavior and combine the relative free energy differences of different mutations and inter residue contact profile analysis to find residues and interactions that are important for the stabilization of different conformational states.

Poster #430   **on-site**

A Pipeline Development of Martini Coarse Grained Representation of Glycosylated Macromolecules

Presenting author: Alam Ahmad Hidayat

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Co-author/s: Mateusz Sikora

The rationale of using coarse-grained (CG) approach in carbohydrate simulations is to provide an access to large simulation time and length scale of key macromolecular processes in glycobiology. Therefore, utilizing our open-source glycan shielding pipeline and its extensive glycan conformers library called GLYCOSHIELD, we aim for developing a reductionist pipeline for grafting N- and O- glycan ensembles on targeted glycosylated proteins and lipids within a Martini representation framework. Starting from available atomistic simulations of glycans in our library, CG potentials in describing improved bonded interactions can be obtained from bottom-up approaches (e.g., iterative Boltzmann inversion and/or inverse Monte Carlo method) by deploying software such as pycgtool in our pipeline. Moreover, the existing glycan parametrization poses major challenges, especially the artificial aggregation propensity evidently observed across carbohydrate simulations in Martini framework studies. This has prompted years of ongoing efforts, including the rescaling the nonbonded interactions in Martini 2 and 3 and the possible introduction of new glycan-specific beads in calibrated Martini parametrizations, two methods to which we will explore in this project. On the other hand, following the recently developed Python-based Martinize2 and Vermouth we expect our pipeline can foster a rapid and easy inclusion of newly CG parametrized glycans from our library and beyond that may be highly valuable for glycobiologist community.

Poster #433   **online**

Harmonizing Nature's Symphony: A Computational Ballet Predicting Calcium-Binding Protein Mutants' Affinity to Ca2+ Through a Physics and Evolution-Based Strategy, Elevating Protein Design

Presenting author: **Pooja Pooja**

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Co-author/s: Pradipta Bandyopadhyay

Embark on a journey through the realms of computational prowess and evolutionary insight as we unveil a groundbreaking method to forecast the binding affinity of calcium-binding protein mutants towards Ca2+. Our meticulously crafted model, enriched by the synergy of physics and evolutionary principles, offers a captivating glimpse into the intricate world of protein design. Through a fusion of molecular mechanics, Poisson-Boltzmann surface area calculations, and charge scaling techniques, we traverse the molecular landscape with finesse, shedding light on the nuanced interplay between structure and function. This predictive framework not only enhances our understanding of calcium-mediated signaling pathways but also paves the way for innovative strategies in protein design. Join us as we embark on this fascinating odyssey, where science meets elegance, and curiosity knows no bounds.

Poster #435   **on-site**

Deciphering Niemann-Pick C Disease: Structural and Functional Perspectives on NPC2-Mediated Cholesterol Transport using Molecular Dynamics Simulations

Presenting author: Smit Patel

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Co-author/s: Nadia Elghobashi-Meinhardt

Niemann-Pick type C (NPC) disease is a deadly autosomal recessive neurodegenerative disorder characterised by the accumulation of cholesterol and other lipids within endolysosomes. This cholesterol storage disorder results from defects in two crucial late endosomal/lysosomal proteins: NPC1 and NPC2. NPC2, 16 kDa Dalton and soluble, plays a role in cholesterol transport by interacting with NPC1 through protein-protein interactions and directly with late endosome and lysosome membranes via protein-membrane interactions. While numerous studies have investigated potential mutations in these proteins and their impact on sterol transport, our understanding of the structure-function relationships of many mutations remains unknown. Recent reports indicate functional changes in these proteins after mutations in NPC1 and NPC2 genes. Additionally, NPC2 is believed to interact with sterol derivatives. The recent high-resolution 4.00 Å (PDB id: 6W5V) structure of the human NPC1-NPC2 complex serves as a valuable starting point for investigating these mutations and their interactions within various lipid bilayer compositions, encompassing different mole percentages of cholesterol molecules. With the help of computational modelling and molecular dynamics (MD), we aim to unravel how these proteins bind to and release cholesterol and its derivatives in diverse lysosomal bilayer membrane compositions. This research represents a crucial advancement in our comprehension of NPC disease, laying the foundation for potential therapeutic interventions.

Poster #447   **on-site**

Brownian Dynamics Simulations of the Bacterial Cytoplasm

Presenting author: **Apoorva Mathur**

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Co-author/s: Ariane Nunes Alves

The cellular environment is densely packed, with up to 40% of its volume occupied by macromolecules. This phenomenon, known as macromolecular crowding, affects the conformations, dynamics, and folding kinetics of proteins. However, most biochemical analyses and simulations are conducted in in vitro conditions, which do not represent the complexity of the environment inside cells. Here, we created models of the bacterial cytoplasm of E. coli and simulated them using Brownian dynamics (BD) simulations to gain mechanistic insights into the dynamics and interactions of proteins in the cellular environment. The models consist of a heterogeneous population of proteins, and their distribution is based on the relative abundance described in an experimentally derived proteome of E. coli. Two types of models were tested, composed of the 30 most abundant proteins, or the 46 most abundant proteins and 2 types of RNA, respectively. Green fluorescent protein (GFP) molecules were added to all systems as well. Experimental diffusion rates obtained for the GFP inside E. coli cells were used to benchmark the models. The GFP diffusion rates observed so far in BD simulations, $0.214E\text{-}2$ Å2/ps and $0.274E\text{-}2$ Å2/ps, are close to the experimentally determined rates of $0.06E\text{-}2$ to $0.14E\text{-}2$ Å2/ps. As a second benchmark, we will compare the protein contacts observed during simulations to a curated experimental E. coli interactome. These models will be used to develop a multi-scale approach combining Brownian and molecular dynamics simulations, enabling the study of dynamics, interactions and conformations for any protein in a crowded cell-like environment.

Poster #451 **on-site**

To Stall or not to Stall? Using Enforced Rotation to Study Dynamics and Energetics of a Nascent Peptide in the Ribosome

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

Macrolide antibiotics, like erythromycin (ERY), inhibit protein synthesis by targeting the exit tunnel of the ribosome. When ERY is bound, ribosomal translation is arrested at specific mRNA sequence motifs, called macrolide arrest motifs (MAMs). Some of the most common MAMs are of the +X+ type, where X indicates any amino acid and + indicates Arg or Lys. The fMet-Lys-Phe peptide stalls in the presence of erythromycin when it is grown amino acid by amino acid. However, stalling does not occur when a tRNA carrying the whole fMet-Lys-Phe peptide is introduced into the ribosome at once, suggesting that the peptide can assume a stalling and a non-stalling conformation. Our unbiased simulations suggest that a free-energy barrier prevents the peptide from moving from between these conformations. In agreement with structural data, we observe the two conformations are stable and differ by a rotation of approximately 180 degrees around the backbone of the Lys amino acid. To check if the transition between the two conformations can take place and which conformations are sampled during the transition, we have driven the system along the rotation angle using the enforced rotation code implemented in GROMACS. Our results show that, both in the presence and absence of ERY, enforced rotation is effective in driving the system from the non-stalled to the stalled conformation. Additionally, we estimated preliminary free-energy profiles along the rotation angle via umbrella sampling combined with Multistate Bennett Acceptance Ratio (MBAR).

Poster #462   **online**

Extending the Stochastic Titration CpHMD Method to AMBER14SB for Acid-Sensing Ion Channels Modeling

Presenting author: João G. N. Sequeira

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Co-author/s: Adrian E. Roitberg, Miguel Machuqueiro

Acid-sensing ion channels (ASICs) are voltage-insensitive, proton-gated cation channels, widely expressed across the central and peripheral nervous systems, that are involved in diverse physiological processes ranging from nociception to brain ischemia [1]. ASICs are activated by extracellular acidosis and ligands can act as antagonists or agonists for the channel's affinity for protons [2]. To discover ASIC activity modulators, one must understand the pH effects on the conformational rearrangement of the protein channel that leads to a change in the cation membrane permeability.

Constant-pH Molecular Dynamics (CpHMD) methods are pivotal to describe pH and its effects on the conformational space of biological systems [3]. The stochastic titration constant-pH Molecular Dynamics (st-CpHMD) method has shown excellent performance over the years [3,4]. Until recently, our implementation of this method only supported the GROMOS 54A7 [3] and the CHARMM36m force fields [4], but we have now extended this method to also support the AMBER 14SB force field, an all-atom force field particularly suited for studying disordered proteins and membrane channels. However, since the charge parameterization procedure of this force field allows side chain charge propagation to the main chain, we propose a small modification to the official ff14SB atomic partial charges to make them st-CpHMD-compatible. Here, we will present our preliminary results using this protocol.

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Poster #466   **on-site**

Base-Pair and Downstream-Structure Free-Energy Differences Estimated from Viral Frameshifting Efficiencies

Presenting author: Annke de Maeyer

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

Ribosomes produce proteins by decoding the nucleotide sequence of mRNA in steps of three nucleotides (codons). Each codon encodes one amino acid and the reading frame is set during translation initiation. A shift of the reading frame results in the synthesis of a different protein. Generally, spontaneous frameshifting is rare, but many viruses have evolved programmed ribosomal frameshifting (PRF) sites, thereby increasing the coding potential of their genome. PRF occurs within a slippery sequence, consisting of seven mRNA nucleotides, which, after frameshifting, group into different triplets and, hence, form base pairs with different tRNA nucleotides. The most common type of PRF is -1 PRF, where the reading frame is shifted by one nucleotide "back" with respect to the original 0 frame. Downstream mRNA secondary structure elements (e.g., stem-loop or pseudoknot) facilitate frameshifting by interacting with the ribosome and impeding translation continuation. As a consequence, the ribosome has enough time to overcome the free-energy barrier between the 0 and the -1 frame. Additionally, structural evidence has shown that stem-loop and pseudoknot interact differently with the ribosome during its movement along the mRNA. Here, we investigate to what extent the two mRNA structured elements affect the free-energy difference between the 0 and -1 frame. In order to estimate free-energy differences associated to changes in base pairing and in downstream mRNA secondary structures, we employ a thermodynamic model (Bock et al., 2019) and apply Bayesian statistics on high-throughput frameshifting efficiency data obtained in an in vivo environment from eukaryotic ribosomes (Mikl et al., 2020).

Poster #470   **on-site**

Non-Universal Impact of Cholesterol on Membranes: Mobility, Curvature Sensing, and Elasticity

Presenting author: **Rainer Böckmann**

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Co-author/s: Matthias Pöhnl, Marius F.W. Trollmann

Biological membranes, composed mainly of phospholipids and cholesterol, play a vital role as cellular barriers. They undergo localized reshaping in response to environmental cues and protein interactions, with the energetics of deformations crucial for exerting biological functions. This study investigates the non-universal role of cholesterol on the structure and elasticity of saturated and unsaturated lipid membranes. Our study uncovers a highly cooperative relationship between thermal membrane bending and local cholesterol redistribution, with cholesterol showing a strong preference for the compressed membrane leaflet. Remarkably, in unsaturated membranes, increased cholesterol mobility enhances cooperativity, resulting in membrane softening despite membrane thickening and lipid compression caused by cholesterol. These findings elucidate the intricate interplay between thermodynamic forces and local molecular interactions that govern collective properties of membranes.
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Poster #479   **on-site**

Intrinsically Disordered Region Amplifies Membrane Remodeling to Augment Selective ER-Phagy

Presenting author: Sergio Alejandro Poveda Cuevas

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Intrinsically disordered regions (IDRs) play a crucial role in organellar remodeling, including homeostatic pathways such as autophagy. However, their precise membrane remodeling functions often remain unclear. The FAM134B/RETREG1, a key ER-phagy receptor protein, presents a long C-terminal IDR containing the LIR motif essential to the recruitment of the autophagic machinery. The present study investigates the FAM134B-IDR through computational modeling and molecular dynamics simulations, elucidating its conformational landscape in solution and membrane-anchored configurations. Our analysis reveals that the IDR ensemble properties vary widely based on tethering. We find that IDRs alone are sufficient to promote and sense membrane curvature. In combination with the RHD, they amplify its remodeling properties, enhancing receptor-clustering and accelerating spontaneous budding. These findings highlight the roles of IDRs within ER-phagy, offering new insights into large-scale membrane remodeling mechanisms.

Poster #480   **on-site**

Multiscale Simulation of Cytochrome P450 Electron Transfer Complexes : The Reduction of CYP17A1 and its Implications for the Regulation of Human Sex Hormone Biosynthesis

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

The cytochrome P450 17A1 (CYP17A1) is a central node in steroid hormone synthesis and is one of a subgroup of cytochrome P450 enzymes that interacts with two redox proteins: cytochrome b5 and NADPH cytochrome P450 oxidoreductase. We applied a multiscale simulation protocol to investigate how human CYP17A1 receives electrons from these two redox proteins upon protein-protein complex formation. Extensive MD-simulations of the complexes were analysed to yield information on the structural rearrangements of the redox partners upon complex formation and on electron-transfer kinetics. Our simulations indicate that both redox proteins can transfer electrons at a similar rate but via different pathways through non-aromatic residues. We also found that the binding modes of both reductases are altered upon embedding the complexes into a phospholipid bilayer and that the binding of the reductases alters the orientation of CYP17A1 relative to the membrane plane. Furthermore, a putative ternary complex of the three proteins was modelled. Our findings show how association to different redox proteins differentially impacts the active site accessibility and the activity of CYP17A1 through conformational rearrangements.

Poster #484   **on-site**

Molecular Dynamics Simulations of the PI3KC3-C1 Complex

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Co-author/s: Annan S. I. Cook, Shanlin Rao, James H. Hurley, Gerhard Hummer

The class III phosphatidylinositol (PI) 3-kinase complex 1 (PI3KC3-C1) is crucial for the initiation of macroautophagy. This complex phosphorylates phosphatidylinositol (PI) into phosphatidylinositol 3-phosphate (PI3P) on the phagophore, which plays an important role in the recruitment of the rest of the autophagy machinery. Cryo-EM structures of the complex bound to the small GTPase Rab1a, which is known to recruit the complex to the membrane, have been recently resolved. Molecular dynamics (MD) simulations are a useful tool to elucidate the activation mechanism of the complex and the interactions between the complex and the membrane. Using this method, we have obtained a stable, membrane-bound model of PI3KC3-C1 in the active conformation. Our simulations shed light on the access of the catalytic subunit VPS34 to the membrane-bound PI substrate. Furthermore, they assessed the stability of the Rab1a interface, where ordered water molecules appear to play a crucial role. In summary, the integration of high-resolution structural data with MD simulations has yielded valuable insights into the activation of PI3KC3-C1.

Poster #487   **on-site**

A Green Approach to Tackling Glycomic Challenges in the Brain and Beyond

Presenting author: **Vidhi Sehrawat**

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Co-author/s: Mateusz Sikora

Glycans, or sugars, cover the surfaces of most membrane and secreted proteins. Rational drug design requires understanding of how glycans alter their function on molecular level. This is supported by comprehensive predictions of glycoprotein dynamics obtained from Molecular Dynamics (MD) simulations, which are computationally expensive. Here, we introduce GlycoSHIELD, a reductionist technique that can be utilized to quickly construct completely glycosylated protein structures on desktop computers.
Modifications in glycan composition in the neurotransmitter receptors have been found to be involved in impairing subunit assembly, protein mobility, cell surface expression, protein stability, and ligand binding. In addition to its effect on neural transmission in many neuropsychological and neurodevelopmental diseases, the efficacy of medical interventions is also affected. We use GlycoSHIELD, with a focus on the GABA Receptor, to address how glycans affect shielding in the functioning of this important membrane protein.

Poster #488 on-site

Investigating Immunoreceptor Oligomerization in Cell Membranes: Insights from Molecular Dynamics Simulations

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Co-author/s: Matthias Pöhnl, Marius F.W. Trollmann, Falk Nimmerjahn, Rainer A. Böckmann

The cell membrane provides a highly diverse platform, facilitating numerous interactions among receptors and between receptors and the lipid environment. By unravelling these intricate interactions, we can get a deeper insight into the mechanisms underlying immune cell activation. This study focuses on two crucial receptors FcγRIII and Mincle, which play pivotal roles in immune response regulation. These receptors compete for binding to the FcϵRγ dimer, commonly referred to as the FcRγ-chain. Investigating the dynamics of these interactions is essential for understanding the intricate mechanisms governing immune cell activation.

FcγRIII, belonging to the Fcγ receptor family, is activated via IgG antibody binding, whereas Mincle can directly engage with pathogens (such as TDM found on bacteria cell membranes). However, neither of these receptors can signal independently; they require association with an immunoreceptor tyrosine-based activation motif (ITAM), which is provided by the FcRγ-chain. A deeper understanding of a possible molecular crosstalk of these receptors could inform the development of novel immunotherapies.

Coarse-grained (DAFT) and all-atom molecular dynamics were both employed to investigate the formation, stability and flexibility of FcγRIII-FcϵRγ and Mincle-FcϵRγ oligomers. Additionally, MD simulations provide high-resolution insights into potential interaction sites between the receptors. Discussed is the possible molecular crosstalk between Mincle and activating Fcγ receptors, as well as the influence of the lipid environment on oligomerization and receptor clustering.

Poster #497 **on-site**

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

Presenting author: **Daniel Sucerquia**

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Co-author/s: Frauke Gräter

When subjecting a protein chain to extreme pulling forces, bonds in the stretched backbone ultimately break. As a most simple assumption, a protein backbone can be considered as a serie of springs each of which carries the same force. 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. We created a package that allows the use of two different methods to obtain the expected results; we proposed one of this methods. We analyse the distribution of energies for a dataset of peptides with three amino acids. We use this information to train a ML engine that predicts the distribution of energies for larger molecules, i.e. proteins.

Poster #505   **on-site**

Comprehensive Bayesian Analysis of DEER/PELDOR Spectroscopy Data

Presenting author: Yixin Chen

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Co-author/s: Catrin Allar, Maria Vicino, Olav Schiemann, Helmut Grubmüller

Pulsed Electron-Electron Double Resonance (PELDOR, also known as Double Electron-Electron Resonance, DEER) spectroscopy is utilized for structural characterization of macromolecular and biological systems, e.g., proteins. DEER/PELDOR measures an oscillatory time-domain signal that depends on the magnetic dipole-dipole interactions between the spin centers, which encodes information about the distribution of distance between the spin centers. Mathematically, inference of the distance distribution from the measured signals is an ill-posed inversion problem. Conventional fitting algorithms including Tikhonov regularization and deep neural networks, despite their utility, suffer from mis-/over-fitting especially when the amount of data is limited, and lack reliable uncertainty assessment. To mitigate these issues, Sweger et al. introduced Bayesian inference into the analysis of DEER/PELDOR data, enabling robust parameter estimation and uncertainty quantification.
Here, we extend the Bayesian approach by developing a comprehensive software package. Compared to Sweger et al.'s work, our package further implements complex models for background and supports consideration of orientation selection of the spin label pair. Using basic Markov chain Monte Carlo (MCMC) sampling techniques, our approach samples the posterior distribution with fast convergence at relatively low computational costs. In benchmark tests using synthetic data, our approach accurately and stably finds the true values of the parameters. Applying to actual experimental data, our approach gives reasonable predictions of distance distributions, compatible with predictions by conventional methods with significant improved overfitting resilience, even when only one set of data is available.

Poster #509 online

Computational Insights into the Effects of pH on β-Glucosidase Stability and Catalysis

Presenting author: Mohannad Jawad Mustafa Yousef

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Co-author/s: Miguel Machuqueiro

β-glucosidases are exo-type glucosyl hydrolases that degrade cellulose in many organisms and play a role in various cell wall functions. The β-glucosidase from Neotermes koshunensis (BgluN) is a widely studied enzyme due to its pH-dependent activity profile that is very interesting for biofuel production. In this work, we use computational methods to study with atomistic detail the effects of altering pH on BgluN stability and catalysis. CpHMD simulations were performed to identify key protonation state changes in the residues near the active site of the protein. Preliminary results on the apo structure showed changes in the protonation states of the two catalytic glutamate residues in the pH range of interest (4–7). Upon substrate (cellobiose) or inhibitor (cellobiose analogue) binding, there is a rearrangement of the H-bond network and new protonation state changes arise, suggesting a possible role in the enzyme activity. The data also suggests that the conformational changes coupled with the protonation changes happening in the BgluN pocket could be modulated by key mutations to facilitate catalysis. These and other related avenues of research are currently being explored in my PhD work program.

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Poster #510   **on-site**

Resolving Coupled and Uncoupled Protein pKa Values Using Computional Alchemy

Presenting author: Carter Wilson

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

The stability, solubility, and function of a protein are governed by its charge and, by extension, the pKa values of its residues. Although these values can be determined experimentally, theory and computation offer a compelling alternative. Here, we apply non-equilibrium alchemical free energy calculations to determine pKa shifts of amino acids in proteins. In these calculations, we explicitly account for couplings between titratable sites. To achieve this, we introduce a thermodynamic-cycle-based formalism and extend an existing microscopic pKa approach to accurately describe this phenomenon. We obtain good agreement with experimental data and achieve an overall average unsigned error of 0.65 +/- 0.08 pK units. A comparison of the accuracies achieved by common pKa predictors reveals that alchemical calculations outperform other approaches.

Poster #522   **on-site**

Automated Parameterization for Reactive Molecular Dynamics Simulations

Presenting author: Eric Hartmann

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Co-author/s: Jannik Buhr, Kai Riedmiller, Leif Seute, Frauke Gräter

In molecular dynamics (MD), classical force fields have enabled remarkable insights into a wide range of molecular systems. In these force fields, atoms are assigned an atom type, and parameters are inherited from this atom type for the duration of the simulation. However, reactions or other events may lead to a change in the chemical environment of an atom, necessitating changes to its parameters. Several methods have been established to deal with changes in an atom's environment. Parameters can be changed dynamically or forces can be evaluated using an entirely different potential, for example neural network potentials.
Here, we extend the recently developed hybrid Kinetic Monte Carlo/ MD scheme KIMMDY to automatically reparameterize the molecular system in between simulations. To achieve this, changes to the connectivity are detected by direct chemical perception, parameter changes are applied to the simulation files and a smooth transition scheme between the parameters is employed. This approach is extensible to further reaction mechanisms which can be added to KIMMDY by supplying a function (e.g. a neural network) that determines the rate for a reaction given a system configuration.
Toy peptide systems are used to demonstrate the simulation of several consecutive reactions without intervention while maintaining highly accurate parameters. Thus, the impact of a given reaction on the relative probability of the ones that follow it can be studied. One application case is the study of mechanoradical migration pathways in load-bearing proteins like collagen.

Poster #525   **on-site**

Parameterizing the Intrinsically Disordered Glycoprotein Lubricin for the Martini 3 Coarse-Grained Force Field

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Lubricin, an intrinsically disordered glycoprotein, plays a pivotal role in facilitating the low-friction in boundary lubrication of synovial joints. Consisting of two globular end domains and a mucin-like, disordered central domain, lubricins tripartite structure is known to be essential for its lubricating function. Notably the 11 different O-glycans that glycosylate the serine, threonine and proline rich central domain are necessary for lubricins low-friction behaviour. However, a comprehensive understanding of the contributions of all three domains is lacking. With approximately 1400 amino acids and 200 O-glycans, modeling complete lubricin proteins at an all-atom scale poses significant challenges. To address this, we parameterize the O-glycans for the Martini 3 coarse-grained force field, enabling a computational exploration of lubricins low-friction properties.

Poster #530   **on-site**

A Self-Organised Liquid Reaction Container for Cellular Memory

Presenting author: Sukanta Mukherjee

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Co-author/s: Enrico Skoruppa, Helmut Schiessel, Jens-Uwe Sommer, Holger Merlitz

Epigenetic inheritance during cell division is essential for preserving the cell identity and the stability of the overall chromatin structure. The 'silent' part of a chromosome, i.e., the heterochromatin, carries one such crucial epigenetic mark that gets diluted on cell division. Here we built a physical model, based on the formation of a bimolecular condensate or 'droplet', that promotes restoration of epigenetic marks. Heterochromatin facilitates formation of the 'droplet', via a process formally known as 'Polymer-Assisted Condensation (PAC), that provides a reaction chamber to carry out different post-translational modifications. We have incorporated the chemical reactions through a particle-based simulation and produced in silico analogue of a cell cycle. The proposed mechanism can stabilize the heterochromatin domains over many cell generations by achieving a faithful epigenetic mark restoration. This mechanism may serve as a general framework for other epigenetic system subject to similar underlying biochemistry.

Poster #532   **online**

Constant-pH MD Simulations of Cytochrome c Oxidase

Presenting author: **Ines Pires**

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Cytochrome c Oxidase (CcO) is the terminal enzyme of the mitochondria electron transport chain, catalysing the reduction of molecular oxygen to water and pumping protons against their concentration gradient. Despite having intricate knowledge of the individual components of this enzyme, there is still information missing to completely understand the function of the proton pumping mechanism of CcO[1]. One such example is the location and role of the proposed Proton Loading Site (PLS), located near the metal cofactors. The loading and unloading of a proton to the PLS have been suggested to be coordinated with electron transport due to the proximity to the metal centres, thus combining the oxidation of the metallic cofactors and the conformation change to accommodate the difference in the electrostatic environment, however, the details of this effect have not yet been reported [2]. In this work, we aim to build a realistic model of Cytochrome c Oxidase using computational methods, through which we can study its proton pumping phenomena. Due to the nature of the system, the use of stochastic titration methodologies coupled with molecular dynamics simulations is key, with constant-pH molecular dynamics[3] (CpHMD) being one such method. It allows the sampling of protonation and deprotonation events of titratable residues throughout a simulation. This means that we can pinpoint which residues can exchange protons, and how variations in the protein's electrostatic profile (resulting from changes in oxidation state) impact proton affinity. We will be presenting preliminary results regarding cofactor parameterization and system setup, which are key steps of this work, considering the important role of these metal complexes in the protein's architecture and function, and the fact that CcO is a membrane protein. Ensuring the proper parameterization and equilibration of both the protein and the membrane it is embedded in is fundamental for setting a solid base on top of which to apply more complex methods with confidence.

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3.   Baptista AM, Teixeira VH, Soares CM. Constant-pH molecular dynamics using stochastic titration. J Chem Phys. 2002;117: 4184–4200.

Poster #533   **on-site**

Variously Crosslinked Collagen Microfibrils Under Force

Presenting author: Johanna Buck

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Co-author/s: Matthias Brosz, Fabian Grünewald, Camilo Aponte-Santamaria, Frauke Gräter

Collagen is a prevalent protein in the animal world and a fundamental component of connective tissues subjected to substantial mechanical forces. To examine the mesoscopic mechanical properties of collagen, we employed a computational model based on the Martini 3 coarse-grained force field and simulated under force. This model can simulate multi-million particle systems on extended timescales which is more than the capabilities of atomistic simulations.

Crosslinks play an essential role in determining the structural and mechanical integrity of collagen and their distribution varies with aging. Various types of crosslinks—the trivalent pyridinoline (mature), and the divalent hydroxylysine ketoimine (immature)—were studied to understand their effects. Our analyses aims to find discrepancies in force concentration between the overlap and gap regions of the collagen microfibrils. Furthermore, we spotlight high-force concentration locations and bonds prone to rupture within large-scale semi-flexible biopolymer networks.

Validation against atomistic reference simulations confirms the model's robustness and reliability. Our findings help to identify the mechanobiological role of crosslinks in collagen and therefore within connective tissues.

Poster #535   **on-site**

Combining Theoretical and Experimental Infrared Spectroscopy of Amid Bands to Discover Structures of Toxic Protein Aggregates

Presenting author: Marvin Scherlo

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

Protein aggregation is a key event for neurodegenerative diseases such as Alzheimer's 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 difficult to be resolved by structure giving experiments like X-ray crystallography, NMR spectroscopy or cryo electron microscopy. Here, we propose a strategy to reach structural insights on aggregation processes on an atomic level by comparing the amid I and amid II band from experimentally measured IR spectra with theoretically calculated ones. As proof 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-Ångström regime on our calculated spectra. Additionally, our calculations show to what extent the observed spectral differences are evoked by variations in the equilibrium structures in comparison to the impact of transition dipole coupling.

Poster #536   **on-site**

Structural Modelling and Dynamic Interaction Network Analysis of Protein-Nucleotide Complexes

Presenting author: **Elias Wippermann**

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Co-author/s: Udo Höweler, Till Rudack

Understanding protein-nucleotide interactions yields crucial insights into fundamental biological processes, cellular signaling, and disease mechanisms. Those interactions often involve conformational changes in both the protein and the nucleotides. Thus, insights into nucleotide-protein interactions by structural modeling and molecular dynamics simulations provide a powerful research tool. We developed a strategy to model different DNA conformations bound to proteins and analyze the dynamic protein-nucleotide interactions within molecular dynamics (MD) simulations. In this regard, contact analysis plays a crucial role in evaluating the stability of molecular complexes, as well as in providing atomic level insights into binding mechanisms. Our developed tool PyContact [Scheurer et al. 2018 Biophysical Journal] automatically distinguish between different types of interactions, including hydrogen bonds, van der Waals interactions, and specific sub-categories. It is applicable to identify contact pattern in static models and within MD simulation trajectories. So far interaction analysis with PyContact is limited to proteins and ions. Here, we present the expansion to include nucleotides. In the course, we also used quantum chemical calculations to derive AMBER force field parameters for phosphorylated 5'-terminal nucleotides not yet included in the Amber force field (AMBER03, nucleic acid parameters from 1996). Finally, an automated workflow for preparing and running simulations including simultaneous contact analysis of protein-nucleotide complexes was developed. This workflow was applied to discover atomic level explanations for biochemical experiments (Grohmann Lab, University Regensburg) that show canonical and uncanonical cleavage in DNA-targets by argonaute proteins, which play a pivotal role in gene regulation.

Poster #538   **on-site**

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

Presenting author: Nicolai Kozlowski

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Co-author/s: Gabor Nagy, Helmut Grubmüller

The accuracy of atomistic molecular dynamics (MD) simulations depends on the accuracy of the force field used. For proteins many force fields have been developed, each in combination with a specific water model. Typically, the combination of a protein force field with another water model is not expected to yield reliable results. Recently, however, the combination of the CHARMM36m force field with the OPC water model has been shown to accurately estimate the compactness and secondary structure content of intrinsically disordered proteins. However, whether CHARMM36m+OPC provides similar accuracy for globular proteins has not been systematically evaluated.

Here, we benchmark this combination on a set of six different globular proteins. To this end, we performed 50 x 1 µs MD simulations per protein using CHARMM36m+OPC and, for comparison, the same simulations using the well-established Amber99SB-ILDN+TIP4P, the original CHARMM36m+TIP3P, and the newer Amber99SB-disp+TIP4P force fields. We compared the generated ensembles first with experimental crystal structures, B-factors, NMR chemical shifts, and folding times; and second between force fields by means of RMSD, radius of gyration, secondary structure content, and conformational kinetics.

We found that the new combination CHARMM36m+OPC predicts experimental observables with competitive accuracy. It excels at generating accurate structural ensembles---especially the compactness of disordered regions---but overestimates timescales for conformational kinetics. Overall, and in combination with previous results for intrinsically disordered proteins, these results suggest that CHARMM36m+OPC should provide competitive accuracy for a wide range of disordered and folded proteins as well.

Poster #539 **on-site**

Asymmetric Steady State Probabilities of Markov Models Explain the Kinetic Asymmetry of ABCE1 Mutants

Presenting author: Malte Schäffner

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Co-author/s: Helmut Grubmüller

The ATPase ABCE1, a member of the ubiquitous ATP-Binding Cassette superfamily, is an essential factor in eukaryotic and archaeal ribosome recycling. A pair of homologous nucleotide-binding domains comprise the majority of ABCE1, each containing a consensus (capable of ATP hydrolysis) nucleotide-binding site, which can be either in an open or closed state. Despite this near symmetry, and quite unexpectedly, the kinetics has been found quite asymmetric: Whereas a E238Q point mutant that impairs ATP hydrolysis in one of the two binding sites reduced the overall turnover rate of the ATPase by a factor of two, as one might expect, a E485Q point mutant that impairs the other site, staggeringly, shows a so far unexplained tenfold increase.
To address this issue, we used Markov models to describe ABCE1 and to study how such asymmetry can arise. Specifically we asked if previously proposed long-range couplings or allosteric interactions between the two binding sites are really required to explain this observation. Indeed, using a Bayesian approach and extensive Markov chain Monte Carlo sampling, we determined Markov models that quantitatively match the measured kinetics as well as additional occupation data, and nevertheless did not require any coupling or allostery beyond the structure-induced property that opening and closing always involve both NBSs. The unexpected fast kinetics of the second mutant is explained in terms of population shift between dominant reaction pathways, which change drastically for the second mutant allowing circumvention of the rate-limiting step present in wild type and first mutant. We expect that this Bayes/Markov approach can help, quite generally, to gain a systematic and quantitative understanding of enzymatic kinetics governed by coupled chemical and conformational dynamics.

Poster #540   **on-site**

A Bayesian Reconstruction Algorithm for Fluctuation X-ray Scattering Experiments

Presenting author: **Michael Maihöfer**

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Co-author/s: Helmut Grubmüller

With the commissioning of high-intensity Free Electron X-ray lasers, experiments can now be performed that allow the capture of scattering images down to the level of individual molecules. This can be used for structure determination of biomolecules and circumvents the traditional limitation of sample crystallization. We focus on Fluctuation X-ray scattering, where such scattering experiments are performed with a dilute solution containing only hundreds of molecules per image, which are captured at timescales far shorter than rotational tumbling times of the molecules. This experiment provides a balance between the ability to observe molecules in a native environment in solution with having as few as possible molecules involved to maximize structural information content.
However, extracting this structural information poses significant challenges, including the unknown orientations of individual molecules and low signal-to-noise ratios inherent in such experiments. To address this, we present a reconstruction algorithm that finds the structure by maximizing the Bayesian posterior probability of observing the measured scattering images.

Poster #552   **on-site**

Fine-Tuning Martini3: Protein-Cosolvent Interactions

Presenting author: Tobias Marcel Prass

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Co-author/s: Michaela Blech, Patrick Garidel, Lars V. Schäfer

Therapeutic monoclonal antibodies (mAbs) are frequently administered at high concentrations, posing challenges for protein stability and solubility. Cosolvents like L-arginine and L-glutamate are known to enhance stability in such conditions, but the precise mechanisms remain unclear. Molecular Dynamics (MD) simulations offer insights into these interactions, yet simulating high-concentration protein systems is computationally demanding. The Martini3 coarse-grained approach makes larger system sizes and time scales accessible but shows different cosolvent-protein interaction patterns compared to all-atom simulations. While on average Martini3 provides reasonable interaction strengths, it lacks residue specificity. Based on these findings, we reparametrize the cosolvent-protein interactions of L-arginine and L-glutamate with the Fab domains of two therapeutic mAbs to match molecular interactions observed on all-atom level.

Poster #553   **on-site**

Isotropic, Semi-isotropic, and Anisotropic Rotational Diffusion of Proteins from Molecular Dynamics Trajectories

Presenting author: Simon Holtbrügge

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Co-author/s: Lars Schäfer

The random rotational dynamics of (bio-)molecules in solution are crucial for processes such as macromolecular assembly or protein-ligand binding as well as for analyzing experiments such as nuclear magnetic resonance (NMR) spectroscopy. The theoretical description of Brownian rigid-body rotation by Favro (1960) provides the foundation to extract the anisotropic diffusion tensor and the three main axes of rotation of a molecule from Molecular Dynamics trajectories. This method is extended to enable fitting diffusion tensors in semi-isotropic or isotropic approximation, e.g. for comparison with experimental data or to accomodate for uncertainties in the data which prevent fitting all six parameters. Best practices are discussed based on model simulations of ideal Brownian rotors and Molecular Dynamics simulations of Ubiquitin.

Poster #555 on-site

Mechanism of Microtubule Assembly: A Coarse-Grained Simulations and Electron Tomography Study

Presenting author: Maksim Kalutskii

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Co-author/s: Helmut Grubmüller, Vladimir Volkov, Maxim Igaev

Microtubules (MTs) are one of the major components of the cell cytoskeleton, which are fundamental to a myriad of cellular processes such as cell division and intracellular transport. These long, hollow cylindrical structures, composed of αβ-tubulin heterodimers arranged in linear protofilaments (PFs), exhibit dynamic instability – a distinctive ability to stochastically transition between growth and shortening. These transitions are intricately linked to GTP hydrolysis. The prevailing hypothesis is that the presence of a stabilizing "GTP cap" enables MT assembly, while the loss of this cap leads to MT disassembly. To explain this behavior, early models proposed an "induced fit" mechanism, postulating that the binding of GTP-tubulin induces PF straightening and renders the MT tip polymerization-competent. In contrast, intrinsically bent GDP-tubulin promotes PF curling and splaying, which causes the MT to depolymerize.

Contrary to this model, recent cryo-electron tomography studies and atomistic molecular dynamics (MD) simulations of whole microtubules MT tips mainly adopt curled and splayed structures, regardless of the nucleotide state. The absence of distinct conformational changes strongly suggests that the mechanism of GTP hydrolysis is likely more complex and that the transition between growth and shortening is primarily governed by the dynamics of the MT tip. Yet, these dynamics are not directly amenable to experiment and remain largely unclear. To tackle this problem, we used a combined simulation and electron tomography approach. Specifically, we introduced a minimal coarse-grained (CG) model of microtubule tip dynamics. The model was optimized against extensive atomistic MD simulations of single PFs (a total of ~80 μs simulated) using a force matching algorithm. Our simulations indicate that bent PFs tend to form metastable clusters with their neighbors regardless of the polymerization state – in agreement with the tomographic reconstructions of growing and shortening MT tips. We demonstrate that both the size and the lifetime of these structural intermediates are strongly dependent on the nucleotide state and the strength of PF-PF interactions. Furthermore, electron tomography indicates a disparity in equilibrium length of growing and shortening MT ends, which our CG model explains by the accumulation of excess lateral stress within PF clusters of GTP-MTs. Overall, our results suggest a new "conformational selection" mechanism of MT assembly, according to which growing (mainly GTP) MT ends favor large clusters of short protofilaments, thus increasing the probability of these clusters to straighten up and complete the MT lattice.

Poster #556   **on-site**

Ribosome Stalling in Presence and Absence of Antiobiotics studied by MD Simulations

Presenting author: Lars V. Bock

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Co-author/s: Sara Gabrielli, 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. Stalling can take place for regulation purposes also when specific sequences are translated. In this case the nascent peptide assumes conformations that are incompatible with the progression of translation. The stalled conformations can lead to homogeneous ensembles and are therefore especially accessible to structure determination by cryo-EM. To address mechanisms of stalling, we use all-atom molecular dynamics (MD) 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) [1,2,3]. 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 resistance determinant [3]. Further, we identified the mechanism used by the ApdP arrest peptide to stall the ribosome while being translated. Finally, we showed that water positions close to ribosome-bound antibiotics, identified by cryo-EM, are relevant at room temperature and that the waters contribute to antibiotic binding by combining machine learning with MD simulations [4,5].

[1] Warias et al. Biophys J 2020, [2] Kolar et al. Nucleic Acids Res 2022, [3] Beckert et al. Nat Commun 2021, [4] Bock et al. Nat Commun 2022, [5] Paternoga et al. Nat Struct Mol Biol 2023

Poster #558   **on-site**

SE(3)^N Equivariant Diffusion Models for the Design of a Small Protein with Trivalent Crosslink

Presenting author: Nicolas Wolf

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Co-author/s: Leif Seute, Frauke Gräter

Generative machine learning is reshaping the field of protein design. State-of-the-art SE(3)^N equivariant diffusion models enable the design of proteins around a broad range of motifs. Here, we investigate how we can use such models to design a scaffold around a trivalent crosslink as it occurs naturally in collagen. To this end, we explore the free energy surface of the crosslinking reaction and develop a method to design a scaffold that facilitates the crosslink formation.

Poster #560   **on-site**

Enzymatic Phosphorylation of Intrinsically Disordered Proteins in Coarse-Grained Simulations

Presenting author: **Emanuele Zippo**

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Co-author/s: Lukas Stelzl

Understanding the condensation and aggregation of intrinsically disordered proteins (IDPs) in a non-equilibrium environment is crucial for unraveling many biological mechanism. We can now address this with residue-level coarse-grained Molecular Dynamics simulations, integrating Metropolis Monte Carlo steps to model chemical reactions. We investigate TDP-43 phosphorylation by CK1D enzyme in simulations, examining patterns of phosphorylation and assessing its preventive role in chain aggregation, possibly associated with neurodegenerative diseases. We find that the degree of residue phosphorylation is determined by sequence preference and charges, rather than the position in the chain. Depending on the sequence context, phosphorylation stabilizes or de-stabilizes condensates. For TDP-43, our simulations show condensates dissolution through phosphorylation, in accordance with experiments. The disordered tail of the kinase Ck1D drives recruitment to the condensates. To further explore the dynamics of non-equilibrium steady-state systems, like our target system, we apply Markov state modelling (MSM). We used MSM to verify the thermodynamic consistency of the phosphorylation step.

Poster #561   **online**

Investigation of Activation Mechanism of Auxiliary Chaperone Proteins from the Hsp40 Family

Presenting author: Krystian Arciszewski

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Co-author/s: Przemysław Domański; Jacek Czub; Bartłomiej Tomiczek

Heat shock proteins (Hsps), also known as stress proteins, comprise a group of proteins present in all cells across diverse life forms. They are induced in response to various environmental stresses, including heat, cold, and oxygen deprivation. Hsps are classified according to their molecular mass, and include Hsp100, Hsp90, Hsp70, Hsp60, Hsp40, and the small Hsp families. Investigating the mechanism of how Hsp40 and other molecular chaperones discern and engage with misfolded polypeptides stands as a fundamental scientific inquiry. Similarly pivotal is unraveling the cooperative interplay between Hsp40 and Hsp70 in protein folding events, it is hypothesized that the EEVD motif, located at the C-terminus of Hsp70, serves as an activating mechanism, facilitating the interaction between Hsp40 and Hsp70. The Hsp40 protein is structurally organized into distinct domains, each fulfilling specific roles in its chaperone function. Foremost among these domains is the J domain, renowned for its pivotal role in orchestrating interactions with Hsp70, thereby modulating its activity. Comprising approximately 70 amino acid residues, the J domain serves as a critical regulator, initiating the ATPase cycle of Hsp70 and enhancing its chaperone activity. In our research, We conducted molecular dynamics simulations using the structure of HSP40 and its mutants to identify the key amino acid residues necessary for regulating the activity of HSP70. Using umbrella sampling molecular dynamics simulation augmented with weighted histogram analysis method, we constructed the free energy profile for dissociation of the J-domain from the C-terminal peptide binding domain (CTD), in the presence and absence of the EEVD. This was done separately for the wild-type (native structure of human HSP40) and its several mutants: K302A, E53A, D93A. This facilitated the proposal of a mechanism for Hsp40 activation and the determination of pivotal amino acid residues involved in this process.

Poster #577 **on-site**

Effects of Solvation and Post-translational Modifications on FUS Condensates

Presenting author: Stefan Sadowski

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Co-author/s: Balázs Fábián, Jan Stuke, Gerhard Hummer

Persistent solid-like assemblies of Fused in Sarcoma (FUS) in the cytoplasm are associated with various pathological conditions such as amyotrophic lateral sclerosis and frontotemporal dementia. Recent studies suggest that post-translational modifications, in particular phosphorylation, of the prion-like domain (PLD) can alter the liquid-solid phase transition of FUS condensates, which may open up new therapeutic strategies. The formation of biomolecular condensates is thermodynamically driven by multivalent but short-lived and weak interactions. To capture the salient physical features of condensates, a complex interplay between solvent and protein interactions has to be carefully modelled. Using coarse-grained molecular dynamics simulations, we study the effects of ionic solvation and phosphorylation of FUS-PLD condensates. Our simulations highlight the impact of different modelling choices on the calculated physical characteristics of condensates.

Poster #579   **on-site**

Nascent Peptide Presence in Ribosomal Tunnel Linked to Long-range Allostery

Presenting author: Hugo McGrath

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Co-author/s: Michal H. Kolář

Ribosomes are biomolecular machines responsible for proteosynthesis. The ribosomal exit tunnel through which the nascent peptide chain escapes is a dynamic environment. It affects the nascent chain as well as being affected by it. This may lead to long-range allosteric modulation. In our previous work we explored how peptide deformylase binding to the ribosome surface can affect the constriction site deep in the exit tunnel through ribosomal protein uL22 and surrounding rRNA. In this poster I will show through the analysis of all atom MD simulations how nascent peptide presence in the exit tunnel may affect the distant ribosomal surface through ribosomal protein uL4.

Poster #580   **on-site**

Enhancing Structural Data of Antimicrobial Peptides Api88 and Api137 with Molecular Dynamics Simulations

Presenting author: Ole Berendes

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

Synthetic antimicrobial peptides Api137 and Api88 are promising lead compounds in antimicrobial research. They share the same sequence, apart from the C-terminus, which is amidated in Api88. Although they both suppress protein synthesis by binding to the ribosome's peptide exit tunnel (PET), recent cryo-EM data suggest that they act by different mechanisms. Api137 traps release factors and prevents dissociation of the peptide chain. Api88 binds to the same sites as Api137 but is more deeply positioned into the tunnel, and the cryo-EM density is less defined. The less defined cryo-EM density of Api88 can be tentatively modelled by three different conformations. Our results from all-atom MD simulations, starting from the three modelled conformations of Api88 in the PET, suggest that Api88 adopts metastable conformational states. To estimate how much the metastable states contribute to the overall conformational ensemble, we computed cryo-EM density maps from the MD ensembles of each state. After that, we combined the computed maps and optimised the weights of the states to maximise the correlation with the experimental map. Interestingly, the optimally weighted MD ensemble displayed an improved correlation to the experimental map compared to the optimally weighted initial conformations. Additionally, we identified the minimal number of structures sufficient to describe the ensemble. Our analysis further shows that one of the three initially modelled conformations contributes most to the cryo-EM density. It shows a slight shift toward the peptidyl transferase centre at the tunnel's beginning compared to the other two structures.

Poster #581   **on-site**

Modeling Biomolecular Cargo in Large Protein Containers

Presenting author: **Tobias Hüfner**

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Co-author/s: Jayashrita Debnath, Balázs Fábián, Peter Njenga Ng`Ang`A, Stefan Raunser, Gerhard Hummer

Tc-Toxins are a family of bacterial toxins that are commonly found in insect and human pathogens. Upon local changes of the pH-value, they inject cytotoxic enzymes into the cytoplasm of their target cells by puncturing their plasma membrane. Structurally, the Tc-Toxin protein complex is composed of a large protein container (1.7 MDa) and the smaller cytotoxic enzyme cargo (30 KDa) located inside the container. While the structure of the former is well resolved through cryoEM experiments, the latter adopts a disordered structure inside the container. From the computational modeling perspective, the structurally unresolved cytotoxic enzyme cargo as well as the large size of the fully assembled Tc-Toxin protein complex are extremely challenging.
To overcome these issues, we model the cytotoxic enzyme cargo inside the protein container by replacing all explicit interactions between the protein container and the cytotoxic enzyme cargo through an effective container potential that is orders of magnitude faster to compute compared to explicit interactions. Then, we use hybrid MD/Nonequilibrium-Candidate-Monte-Carlo (NCMC) sampling to couple the cytotoxic enzyme cargo to the effective container potential, which provides an excellent distribution of all-atom starting structures. From the subsequent microsecond time-scale equilibrium trajectories of the all-atom cytotoxic enzyme cargo, we study the internal pressure inside the protein container and as well as the formation of secondary structure elements. Finally, we characterize the response of the system due to changes of protonation states and thus provide atomic details on the injection mechanism.

Poster #583   **on-site**

Investigation of Gatifloxacin Permeation Through Outer Membrane Porins of Gram-Negative Bacteria

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Co-author/s: Abhishek Acharya, Ulrich Kleinekathöfer

Gram-negative bacteria have a distinct outer membrane that creates a formidable barrier to antibiotic permeation. Porins act as diffusion channels, providing a pathway for several antibiotics. Although numerous studies have explored antibiotic permeation through experimental and simulation approaches, a deeper understanding of the underlying mechanisms is still necessary. This investigation examines the permeation of fluoroquinolone - Gatifloxacin through OmpF, a porin found in Escherichia coli, and its homolog OmpE35 in Enterobacter cloacae. Classical molecular dynamics simulation and applied field simulation were used to investigate the dynamics of the pore without an antibiotic. Temperature Accelerated Sliced Sampling (TASS) has improved sampling efficiency in antibiotic permeation, resulting in more accurate free energy calculations. Free energy calculations were used to identify the permeation pathways in both porins, which share a significant 77.1% sequence identity. Our simulations revealed distinct differences in the free energy of the antibiotic within both porins, prompting a thorough examination of the interactions along the permeation pathways. This study comprehensively examines the permeation of antibiotics across porin orthologs, providing insights into their properties and potential modifications to enable permeation through a broader range of diffusion channels.

Poster #585   **on-site**

Feedback Between Experiments and Simulation Force Fields for Intrinsically Disordered Proteins

Presenting author: **Miloš Ivanović**

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Co-author/s: Valentin von Roten, Andrea Holla, Benjamin Schuler and Robert B. Best

All-atom explicit solvent molecular dynamics (MD) simulations are a powerful tool for investigating and visualizing the dynamics and interactions of biomolecules. While the accuracy of MD simulation force fields of intrinsically disordered proteins (IDPs) has increased significantly over the last decade, there is still room for improvement [1]. This is particularly true for simulations of phase-separated systems, where the high concentration of residues [2] increases the likelihood of accumulation of small simulation errors.
Here, we first tested force fields using MD simulations of sixteen IDPs of identical length, selected from naturally occurring sequences with large differences in sequence composition, against single-molecule FRET data. All simulations were performed both with and without fluorophores to ensure a rigorous comparison with experiments. Our first finding is that the influence of the fluorophores themselves is smaller than the statistical sampling error, suggesting that the dyes used are minimally perturbing the system. The absolute agreement between simulated and experimental FRET efficiencies is also remarkably good in most cases, allowing us to identify from the outliers which specific interactions in the force field are most problematic. We have performed and used a series of osmometry experiments to improve the simulation parameters for these interactions and are currently validating these improvements.

[1] Best, Curr. Opin. Struct. Biol 60 27-38 (2020)
[2] Galvanetto*, Ivanović*, Chowdhury, Sottini, Nüesch, Nettels, Best, Schuler; Nature 361, 355-360 (2023)

Poster #586   **on-site**

The N-terminal IDR of SUMO Modulates its Interactions in a Crowded Environment

Presenting author: Jan Stuke

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The structure of small ubiquitin-like modifier (SUMO) proteins consists of a ubiquitin-like core fold and a short N-terminal intrinsically disordered region (IDR). SUMOs can be covalently attached to target proteins via isopeptide bonds, similar to ubiquitin. This posttranslational modification, called SUMOylation, can modulate the interactions, location, conformation, and solubility of its substrates. Notably, proteins with SUMO interacting motifs (SIMs) can bind to the SIM binding site of SUMO. SUMOylation is involved in various cellular processes, one of them being the pathological aggregation of intrinsically disordered proteins (IDPs) in condensates. However, the molecular details underlying the effect of IDP SUMOylation on the properties of condensates remain elusive. We study the interactions of SUMO in a crowded molecular environment with molecular dynamics (MD) simulations. As model system, we utilize homogeneous dense solutions of SUMO1, SUMO2, and ubiquitin at atomistic resolution. We vary protein concentration, perform structural truncations, and describe the resulting changes in interaction and diffusion properties. We find that the N-terminal IDR of SUMO, which is not present in ubiquitin, modulates interactions – especially for residues proximal to or within the SIM binding site. In turn, the IDR impacts protein diffusion and increases the solubility.

Poster #587   **on-site**

Efficient Generation of Disordered Protein Ensembles at Atomic Resolution: An Easy-to-Use Implementation of Hierarchical Chain Growth

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Efficiently generating accurate models of disordered proteins at atomic resolution is a long-standing problem in computational biophysics. We present an adapted version of the hierarchical chain growth (HCG) method that can be applied to arbitrary sequences in a fast and user-friendly manner via a web-application. In HCG, we draw peptide fragment conformations from an exhaustively sampled fragment library and assemble them hierarchically in a Monte Carlo chain growth scheme. The assembled chains accurately sample the local peptide structure, exhibit large global structural variability across the ensemble, and avoid the chain collapse observed in atomistic molecular dynamics (MD) simulations with unbalanced force fields. The present implementation draws from an exhaustively sampled library of dimer fragments, totalling 20^2 residue combinations. We show that by using HCG we assemble chains that accurately recover the local structure sampled in MD simulations. The chain extension, however, tends to be somewhat overestimated. Using the web-application, moderately sized ensembles can be generated within seconds. We recommend using these for visualization, as diverse starting structures for MD simulations, and as input for ensemble refinement. An HCG implementation for arbitrary sequences opens up possibilities for other chain growth applications. For example, it can be used to quickly generate structures of dense solutions of disordered proteins for MD simulations of phase separated systems. Furthermore, we are developing a method of sampling constrained flexible chains (e.g., loops) by using HCG for backmapping from coarse-grained simulations.

Poster #589   **on-site**

Role of Oligomerization State in Conformational Transitions of Human Platelet Phosphofructokinase

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Glycolysis is a crucial metabolic pathway which is subjected to regulation via a range of mechanisms and the disturbances of which have been linked with disease. The enzyme Phosphofructokinase-1 (PFK1), catalyzes the rate-limiting conversion of fructose-6-phosphate to fructose-1,6-bisphosphate, is a key flux controller of the glycolytic pathway. However, a full mechanistic understanding of this regulation, which has been suggested to involve changes in the oligomerization state of the enzyme, is still lacking. Here we perform fully atomistic molecular dynamics simulations of the human platelet PFK1 isoform (PFKP) in several different oligomerization and ligand-binding states. Our extensive simulations show that the conformational flexibility of functionally relevant parts of the PFKP structure is significantly altered by changes in the oligomerization state. Moreover, by delivering a state-dependent correlation network analysis, the work forms a basis for a deeper understanding of the allosteric regulation of PFKP.

Poster #590   **on-site**

Exploring the Evolutionary Stability of the Peptidyl Transferase Center in Ribosomes Using All-Atom and Coarse Grained Simulations

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The ability of ribosomes to catalyze peptide bond formation is attributed to the peptidyl transferase center (PTC), a catalytic site composed solely of ribosomal RNA (rRNA). Within the ribosome, a structurally symmetric region envelops the PTC, and this feature has been observed consistently across diverse species. This intriguing symmetry hints at an ancient evolutionary origin, suggesting that over billions of years, the PTC has evolved through the accretion of rRNA and ribosomal proteins. However, the precise roles of ribosomal proteins (rProteins) and rRNA in conferring stability to the PTC remain elusive, with the prevailing assumption that the PTC has become less flexible over time. To explore this hypothesis, we conducted all-atom (AA) and Martini coarse-grained (CG) molecular dynamics simulations on two ancestral ribosomes, reconstructed from a modern ribosomal template. We focused on PTC constructs incorporating various rProtein fragments. The AA simulations reveal striking structural similarities between ancestral and modern PTCs. Furthermore, the interactions between rProteins and rRNA appear to play a crucial role in maintaining the conformational stability of the PTC, potentially enhancing the specificity of peptide bond formation. Our findings provide valuable insights into the molecular mechanisms underpinning the evolutionary stability of the PTC within ribosomes.

Poster #591 **on-site**

Exploring the Interactions of Multivalent Ligands with C-Type Lectin Homotetramers

Presenting author: Yu Lin Ho

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Dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN), a pivotal member of the C-type lectin family, plays a critical role in the immune response. It recognizes various pathogens, such as viruses, bacteria, and fungi, in particular by binding to high-mannose-containing glycoproteins. Notably, this recognition mechanism is exploited by certain viruses, including SARS-CoV-2, to invade host cells. Therefore, disrupting the interaction of DC-SIGN with high-mannose-containing glycoproteins is a promising strategy to inhibit host cell invasion.

This study demonstrates the development of multivalent glycomimetic antagonists for the homotetrameric DC-SIGN protein, resulting in improved avidity compared to monovalent antagonists. The improvement in binding affinity is achieved by carefully considering various aspects of the design of multivalent inhibitors. The apparent simplicity of linking multiple monomers is contrasted by the complexity of determining the type and length of the linkers. In particular, the linker length is a crucial design constraint, as it influences the overall shape and functionality of the compound. Traditionally determined experimentally, our study proposes computer-aided design as an efficient and cost-effective method to determine suitable linker lengths. Our interdisciplinary approach, combining experimental results with computational insights, facilitates the design of multivalent antagonists for DC-SIGN and thus contributes to developing novel therapeutic strategies.

We employed a combination of ColabFold and MODELLER to model the homotetrameric structure of DC-SIGN. To assess the length dependence of the linker behavior, we performed MD simulations of isolated linker systems of different lengths and analyzed them for various parameters, including persistence length. The results obtained for the linkers allowed us to draw valuable conclusions about the structural and functional properties of the multivalent DC-SIGN inhibitors to be developed. This computational approach significantly contributes to deepening our understanding of DC-SIGN and its potential as a target for drug development.

Poster #592   **on-site**

Coupling the Role of Lipids to the Conformational Dynamics of the ABC Transporter Pgp

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Co-author/s: Lars Schäfer

The ATP-binding cassette (ABC) transporter P-glycoprotein (Pgp) energizes the efflux of compounds through the plasma membrane and it is implicated in multidrug resistance in cancer. Its portal helices exhibit two conformations—straight and kinked—in high-resolution structures solved in detergent and nanodiscs, respectively. However, at the atomic level, the link between these two alternative inward-open conformations and Pgp function is unclear. We employ MD simulations to explore the dynamics of the two conformers in hepatocyte-like membranes and found that the access to the substrate cavity of the kinked conformer is restricted. Moreover, the cavity's volume and dynamics, influenced by cholesterol and ATP, differ between the conformers. Our findings suggest that the straight conformation precedes the kinked in the series of conformational transitions that underlie the functional mechanism, with the kinked conformer potentially playing a role in preventing substrate reuptake. Remarkably, in our unbiased simulations a spontaneous straight to kinked transition of one TM helix was observed. Our study highlights the lipid environment's impact on Pgp structural ensemble and elucidates the functional significance of its two inward-open states, shedding light on Pgp's overall mechanism.

Poster #593 on-site

Molecular Dynamics Simulations Coupled On-The-Fly to Experimentally Determined Helical Content for Interpretation of Circular Dichroism Data

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Circular dichroism (CD) spectroscopy enables determination of protein secondary structure content, albeit providing only ensemble- and residue-averaged data. Molecular dynamics (MD) simulations enable atomistic interpretation, but frequently suffer from force-field inaccuracies and incomplete sampling. Integrating MD simulations with CD addresses these limitations, enabling atomistic interpretation, while the CD data improve force-field and sampling issues related to inaccurate secondary structure propensities.
We develop a method to couple MD simulations on-the-fly to CD-derived secondary structure content by applying harmonic restraints that ensure agreement with experimentally derived secondary structure content. Our differentiable forward-model is based on the Define Secondary Structure of Proteins (DSSP) algorithm. Current implementation of the restraints is acting on a single replica, however we aim to account for the ensemble-averaged data by implementing ensemble restraints with commitment to the maximum entropy principle following the parallel-replica approach, as demonstrated in previous work for refining ensembles against small-angle scattering data. Here we present MD simulations of a small test peptide, $(AAQAA)_3$, with restraints on the α-helical content. Coupling of MD simulations to CD-derived secondary structure content will be especially useful for structural ensemble refinement of proteins and peptides with intrinsic disorder, for which force-fields often lack accurate secondary structure propensities.

Poster #594   **on-site**

Resolving the Mechanism of Transmembrane Hairpin Insertion on the Timescale of Seconds

Presenting author: Hendrik Jung

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Co-author/s: Stefan Schäfer, Gerhard Hummer

We recently proposed the massively parallel machine learning (ML) algorithm "AI for Molecular Mechanism Discovery" (aimmd) [1]. The algorithm combines transition path sampling, concepts from statistical physics, and deep learning to autonomously learn the succinct features of a transition in an iterative and self-consistent manner. Aimmd can steer and learn from an almost unlimited number of parallel MD simulations, becoming increasingly efficient in learning the transition dynamics with increasing degree of parallelization. Aimmd thereby makes previously inaccessible timescales accessible to MD simulations.

Here, we present the results of the application of aimmd to the rare membrane insertion of a β-hairpin, which is part of the large β-sheet that gasdermin oligomeres form when creating membrane pores during pyroptosis. The aimmd algorithm was able to efficiently sample the insertion dynamics taking place on the timescale of seconds or longer, generating a total of 300 unbiased transitions. Furthermore, an analysis of the knowledge about the transition encoded in the trained neural network and low-dimensional projections of the collected ensemble of transitions show that the neural network successfully learned the importance of the lipids for the insertion. In addition to the lipids, the orientation of the β-hairpin with respect to the membrane and the formation of the β-turn are identified as key determinants of the insertion. Finally, the neural network and the collected equilibrium ensemble of transitions were used to estimate the insertion rate in a computationally efficient manner. Our results show that the insertion of a single β-hairpin into the membrane is an energetically highly unfavorable rare process, indicating that the pore formation by gasdermin oligomers proceeds in a cooperative fashion.

[1] Jung, H. et al. Machine-guided path sampling to discover mechanisms of molecular self-organization. Nat. Comput. Sci. 3, 334–345 (2023).

Poster #595 on-site

Predicting Atomic Models of Ligand Binding Pockets Based on Sparse Cryo-EM Densities

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A key part of the development of target specific drugs is gaining insights into the protein-substrate binding interface. For this, the mode of substrate binding, stabilizing interaction interface and mechanism of substrate conversion need to be understood. Resolving and analysis of novel ligand protein structures provides a starting point for drug development. Here, we present a strategy to model and refine ligand binding pockets with sparse densities from cryo-EM experiments by combining molecular dynamics simulations, protein docking algorithms, and protein-ligand interaction analysis. First, we identify key interaction pattern and conformations of the specific ligand or chemically similar ligands by analyzing resolved structure of protein-ligand complexes deposited in the protein data bank. Therefore, we use our in-house developed tool for contact analysis, PyContact (Scheurer et al. Biophysical Journal 2018) and the software package MAXIMOBY (CHEOPS). Incorporating the identified interaction pattern we perform feature guided docking of ligand to the apo structure employing the docking software HADDOCK (Dominguez et al. 2003). Then, the resulting holo-structure is refined using the cryo-EM density map employing molecular dynamics flexible fitting (Trabuco et al. 2008) iteratively with Phenix real space refinement to optimize the model validation statistics. The final structure is an analyzed regarding its ligand-protein interactions. Here we showcase the strategy at the case example of a bound inhibitory ligand of a bacterial ABC-Transporter.

Poster #596   **on-site**

Exploring the Conformational Transitions of Adenylate Kinase in a Crowded Milieu

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Co-author/s: Štěpán Timr

Inside living cells, enzymes are exposed to a highly crowded and complex environment. These conditions, which are far from those in conventional in-vitro assays, can alter enzyme activity in non-trivial ways. To understand these effects, detailed insights from molecular simulations are highly desirable.

In this work, we employ all-atom molecular dynamics (MD) simulations to investigate the impact of molecular crowding on adenylate kinase (AK3L1) as a model enzyme. We describe how crowding affects conformational changes and substrate binding, which are linked to enzyme activity.

The results help to rationalize previous experimental observations reporting altered kinetic parameters of adenylate kinase in the presence of crowding. Our study is a step towards a better understanding of enzyme behavior within the complex milieu of living cells.

Poster #600   **online**

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

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Coronaviruses are a diverse family of enveloped RNA viruses. There are seven human viral species (229E, OC43, NL63, HKU1, SARS - CoV, MERS and SARS – CoV2) identified till now. Human CoVs cause mild to severe respiratory system infections. Till now, there is no available broad spectrum antiviral and there are ongoing efforts to find a suitable one. 3CLpro or main protease (Mpro) is a suitable target for deigning viral inhibitors. With the aid of different computational methodologies, we aim to investigate binding site dynamics, energetics, druggability and cryptic sites (hidden pockets "invisible" in the apo structure) 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 Langevin rotamerically induced perturbations (L-RIP) MD approach. The predicted cryptic pockets are the loop region covering the entrance of binding site, the small loop containing MET49 above the active HIS41 and the dimerization interface. 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 sites show different flexibility regions with different shape and size where NL63 and HKU1 show larger volumes. The dynamics of protease may be genus' specific where NL63 (Alphacoronaviruses) behave differently from other Betacoronaviruses. We are in need to take such dynamic behavior in our design of new coronaviral drugs and alleviate any concerns about drug resistance as well.

Poster #606   **online**

The C282Y Mutation in Hereditary Hemochromatosis: Structural and Functional Implications Investigated by Molecular Dynamics Simulations

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Hereditary hemochromatosis (HH) is an autosomal recessive disease characterized by an improper regulation of iron uptake, leading to an iron overload in different specific organs. The responsible of HH is a mutated protein called HFE, a class I major histocompatibility complex (MHC) homolog, formed by two domains: the alpha1,2 MHC-like domain and the alpha3 immunoglobulin-like domain. The predominant mutation in HH is the C282Y (C260Y in the mature protein) in the alpha3 domain, which converts a cysteine residue in a tyrosine, breaking a disulphide bond and affecting the association of HFE with a beta2-microglobulin (beta2m) chain that prevents its externalization at the cell surface. wt HFE competes with iron-loaded transferrin (Tf) for binding to the transferrin receptor (TfR) at the cell surface. HFE interferes with Tf binding site on TfR and regulates iron absorption. The mutated protein is not able to bind TfR and the regulation fails, causing the iron overload.

In this work, we tried to give insight into the effects of C282Y (C260Y) mutation on the HFE structure and on its interaction with the beta2m domain, by means of molecular dynamics simulation technique. We followed the evolution of four systems: the HFE-beta2m complex and the HFE chain alone, in the wt and mutated form, accelerating the structural changes by means of a temperature increment.

The mutated tyrosine comes to be in a hydrophobic environment and try to move towards a more polar one enlarging the barrel, helped in this by the broken disulphide bond. Its partial exposition to the solvent perturbs the molecular surface, affecting the interaction with the beta2m domain and of the latter with the MHC-like one. The main effect is the exposition of Trp60 residue of beta2m, known to be fundamental for the association of beta2m with HFE chain.

Poster #607   **on-site**

Effects of Protein Concentration on Intra- and Intermolecular Contacts of p53 N-terminal Transactivation Domain (TAD)

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Co-author/s: Gabor Nagy and Helmut Grubmüller

The tumour suppressor protein p53 (p53) participates in various cellular activities like arresting cell division upon DNA damage, DNA repair, and initiating programmed cell death by controlling the expression of key apoptotic genes. P53 is often referred to as "guardian of genome" as it maintains "genomic integrity" by stopping the cell cycle when oncogenes are expressed aberrantly and elimination of cells that suffered irreparable DNA damage. The N-terminal residues of P53 form its intrinsically disordered transactivation domain (TAD), which can be further subdivided into TAD1 and TAD2. Due to the importance of p53-TAD and its subdomains, it has been studied extensively using circular dichroism (CD), nuclear magnetic resonance (NMR), and small angle X-ray scattering (SAXS) etc. However, intrinsically disordered proteins (IDPs) are particularly sensitive to experimental conditions. The measurement conditions are optimised for the experimental methods, which often poses an obstacle for comparing results about IDPs and may lead to conflicting results. Similar discrepancies were also observed in p53-TAD. We hypothesized that the conflicting conclusions about the p53-TAD secondary structure are caused by different concentrations used across various experiments. To test this idea, we performed molecular dynamics simulations at protein concentrations ranging from 3.2 to 12.8 g/L and analysed potential structural and secondary structure changes. Our preliminary results suggest that the secondary structure does not change significantly across different concentrations of p53-TAD, however, the intramolecular and intermolecular contacts change with concentration.

Poster #608 on-site

Probing the Accuracy of Forcefields on the Structure and Kinetics of Disordered peptides

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Co-author/s: Lillian Otteson, Crystal Ottoway, Gerdenis Kodis, Wenwei Zheng, Sara M. Vaiana and Helmut Grubmüller

Intrinsically disordered proteins (IDPs) are a class of proteins that perform their functions without folding into particular stable structures. Dynamics and formation of transient structures in IDPs and intrinsically disordered regions (IDRs) of more complex proteins are often vital for biological processes in living organisms, as well as for understanding how disordered proteins work in general.

Due to their inherent flexibility, IDPs and IDRs occur as ensembles of different and rapidly interconverting conformations, which poses particular challenges for studying them experimentally or computationally. Experimentally, IDPs are more sensitive to environmental conditions, are hard to crystallize, and limit the available methods of study to either single-molecule methods, or methods that provide ensemble-averaged information. Computationally, IDP and IDR structures have to be represented as conformational ensembles that are harder to obtain, and often require more experimental information to confirm and validate. Molecular dynamics (MD) simulations can capture and their inherent flexibility associated with IDPs, and thus are computational methods very suitable to study these molecules. However, the structure and dynamics IDPs and IDRs in MD simulations strongly depends on the applied parameter set (forcefield). Further forcefield inaccuracies can affect IDPs differently depending on their length and sequence composition.

Here, we probe the accuracy of several protein forcefields that were reported to produce reliable IDP ensembles. The accuracy of each forcefield is determined by predicting experimental observables from MD generated IDP ensembles and comparing to experimental circular dichroism (CD) spectra, small angle X-ray scattering (SAXS), and nuclear magnetic resonance (NMR) chemical shift data. For this analysis we selected five model IDPs of differing size and estimated secondary structure composition. Further, we probe the accuracy of IDP kinetics of a set of 30 AGQ-repeat peptides produced by MD simulations using three selected forcefields. The dynamics of these peptides were previously studied using photo-induced electron transfer (PET) experiments, a fluorescence spectroscopy method that probes intramolecular contact dynamics of proteins. Our results indicate that the choice of the forcefield has a considerable effect on the compactness and transient secondary structure propensities of MD-generated IDP ensembles. In addition, the tested force fields tend to overestimate the rate of contact formation rates AGQ repeat peptides.

Poster #612   **on-site**

Gating Mechanisms of the Slo1 BK Channel

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

Slo1 is a potassium channel that belongs to the group of 'big potassium', or BK channels. BK channels have an unusually high conductance rate for potassium ions, on the order of ~100 pS, and are activated synergistically by Ca^{2+} ions and voltage. For Slo1, CryoEM structures of its Ca^{2+}-bound and Ca^{2+}-free states are available. However, Slo1 in the Ca^{2+}-free - supposedly closed - state lacks a constriction that would prevent the passage of potassium. In the present work, we elucidate the functional states of the available CryoEM structures of Slo1 in equilibrium and under applied voltage using MD simulations. Furthermore, by varying the lipid composition of the membrane, we investigate the hypothesis of the pore block by lipids as a closing mechanism, and study the accompanying conformational changes in the channel.

Poster #613 on-site

Effect of Two Small Molecules in the Gating Modulation of TREK1 Channel

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

TREK1 is a K+ mammalian channel that causes leak currents, which control the negative resting potential in the cell membrane and, therefore, it is a potential therapeutic target for the treatment of neurological disorders. The gating of this channel converges in the narrowest part of the pore: the selectivity filter (SF). There are some hypotheses about the gating modulation of TREK1; namely: the dynamics of the loops that link the pore helices, and the formation /rupture of hydrogen bond (HB) networks behind the SF. Recently, two small molecules (Q6F and Q5F) were reported as activators of TREK1 by increasing its open probability due to the stabilization of the SF. Here, we ask what the effect of these ligands is in light of the previously proposed modulation mechanisms of TREK1 gating, compared with the apo channel. We found that Q6F exhibits the strongest effect, increasing the probability of permeation which is directly related to distortions in the SF. This ligand modifies the dynamics of a threonine sidechain at the bottom of the filter, which preserves the HB network behind the SF and prevents the flipping of the carbonyl in the S3 binding site. The effect of the ligand is also correlated with the decreasing of the number of water molecules behind the SF, the restriction of a tryptophane sidechain in an acute angle, and the presence of lipid molecules in the pocket, which together keep the pocket rigid and dehydrated. The hypothesis related to the loops on the top of the SF is less likely since its rigidification is weakly correlated with the non-permeation events in the channel, and there are inactivation events (C-type-like) on the top of the filter even with the presence of the molecules. Our findings suggest that the most modulated gate is the one involving the carbonyl flip at S3, while the prevention of dilation at the top of the filter is affected to a lower degree, but we do not discard a possible coupling between both. Besides, these results open the door for the rational design of ligands that optimize these gating mechanisms, as well as the possibility of modulating related channels in a similar way.

Poster #614   online

Superoxide Production in Protein Complexes

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In recent decades, the impact of low-frequency external magnetic fields (ELF) on biological cells has been studied. Biological effects of the magnetic fields on cells and tissues are non-thermal. For this reason, the potential effects of low-frequency magnetic fields on human health are being extensively studied. A number of observations indicate the antitumor properties of ELF that have an antiproliferative effect and lead to an increased apoptosis of cancer cells. It has been suggested that a part of the biological effects of ELF is due to the increase in the concentration of free radicals such as reactive oxygen species. Finding the main site of the effect of ELF on the concentration of reactive oxygen species is a significant issue. An important source of the production of reactive oxygen species in cells is the production of superoxide in the electron transport chain in mitochondria. Our purpose is to investigate the possibility of the effect of low frequency magnetic fields on the amount of superoxide production in protein complexes 1 and 3 of the electron transport chain through the radical pair mechanism. For this purpose, we use molecular dynamics simulations (MD) and density functional theory (DFT). Here, we present our results obtained for the different spin states of the active sites and how these relate to the probability of superoxide formation.

Poster #617   **on-site**

Modeling DNA Deformation Energy in DNA-Protein Interactions

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During sequence-specific binding of DNA-protein interactions, there are two main mechanisms for the recognition of target DNA, namely base (direct)- and shape (indirect)-readout. The former involves the recognition of binding site via the formation of hydrogen-bonds and other contacts between the amino acids in the protein and the chemical groups of the DNA. On the other hand, shape-readout makes use of the sequence-dependent flexibility features of DNA where the ensemble of conformations that the oligonucleotide attains provides steric compatibility and promotes protein binding. In the present study we employ a multivariate Ising model to compute the ensemble of thermodynamically consistent deformation energies acquired for sequence-specific DNA conformations considering a nearest-neighbor coupling between base-pair and base-pair-step helical parameters with harmonic potentials determined by the different backbone states BI/BII. Using this description for DNA deformations allowed us to characterize the readout mechanism of 30 distinct DNA-protein systems by calculating the relative entropy between the ensembles obtained for unbound and bound DNA. Additionally, the model enables a rapid computation of binding free energies across different sequences as well as the determination of an optimal DNA sequence for a specific binding pose given by its helical parameters. These features where applied to the FIS-DNA complex, where it was experimentally demonstrated that changes in the sequence outside the binding regions can have a significant impact in the binding free energy, resulting in the ability to quickly asses the best binding sequences with good agreement with experiment.

Poster #735   online

Unveiling the TP53-CDK1 Axis to Target CDK1 in Breast and Lung Cancer via Integrative Multi-Omics, Molecular Docking and Molecular Dynamics Simulation

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Based on epidemiological evidence, a connection emerged between breast cancer and lung cancer. To investigate this, we carried out a comprehensive multi-omics analysis to identify and target a common key cancer proliferator. From multiple transcriptomics datasets and curated gene lists, we filtered 75 high-confidence differentially expressed genes (DEGs) commonly upregulated in both malignancies. Protein interaction network analysis of the DEGs using Cytoscape software highlighted cell cycle controllers CDK1 and CCNB1 as pivotal hub genes. We extensively validated their overexpression, prognostic potential, and tumor-specific rewiring across breast and lung cancers using TNMplot, KM Plotter, and TIMER2.0 web portals. We further compared their correlation with TP53. Both CDK1 and CCNB1 showed upregulation in TP53 mutation, but CDK1 was found to be highly tumor-specific with a strong expression correlation with TP53 mutation status and less involvement in other cellular functions compared to CCNB1. Therefore, we carried out molecular docking screening of commercially available cyclin-kinase inhibitors against CDK1, targeting key residues based on literature evidence. THZ2 emerged as the ideal compound interacting with all the important key residues, which was further validated through molecular dynamics simulation. Through our comprehensive analysis conducted across multiple platforms, we obtained compelling evidence for targeting CDK1 as a prognostic biomarker, affirming its potential as a therapeutic target downstream of TP53 mutations, where THZ2 holds high inhibitory potential.

Poster #737   **online**

Role of Sequence Dependent Information Transfer in Target Search Dynamics of DNA Binding Proteins

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DNA, the blueprint of life, is a double-stranded helical structure composed of nucleotide base pairs that encode the instructions for building and maintaining living organisms. The role of DNA sequence in its conformational dynamics and target search mechanism of DNA binding proteins (DBPs) unveils a captivating symphony of molecular interactions and cellular choreography. The sequence of DNA bases is not only the sole determinant of DNAs behavior within cells but also modulates its structure and flexibility, impacting molecular motions and structural changes. Specific DNA sequences can adopt distinct conformations, such as hairpins, loops, or cruciforms, by exploiting the inherent flexibility of the DNA backbone and the interactions between adjacent base pairs. These conformational transitions enable DNA to interact with other molecules (DBPs) and participate in intricate cellular processes that rely on the target site recognition located on the DNA involves the dynamic exploration of the vast genome to locate and bind to their specific binding sites. This process is inherently challenging due to the enormous size of the genome and the DNA sequence plays a fundamental role for efficient and accurate target recognition. Our pursuit involves unraveling the intricate relationship between DNA sequences and the search and recognition binding modes adopted by DBPs as they navigate DNA, pinpointing and binding to their designated sites. The information of conformational transition and the flexibility of the target site propagates to distant sites through DNA bases which creates a rugged energetic landscape around binding sites. The search process involves continuous transition between search and recognition mode of the protein which depends on the inherent character called frustration of the protein. The kinetics of target search dynamics is intricately tied to the rugged landscape, while the pace of recognition primarily hinges on the free energy barrier associated with transitioning between the DBP's search and recognition binding modalities. We also hypothesized that the ruggedness of energetic landscape depends on sequences of target sites often different for different proteins and the proximal DNA sequences are evolutionary designed in order to balance between rugged energetic landscape associated with target DNA sequence and transition between two modes of protein (intrinsic property).

Poster #741 online

Deciphering the Synthase Mechanism of a GH172 Enzyme on the Inulobiose-DFA I Conversion using QM/MM Metadynamics

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Difructose dianhydride I synthase/hydrolase (αFFase1) is a member of the family 172 of glycoside hydrolases which catalyzes the reversible transformation of inulobiose into difructose dianhydride I (DFA I). This transformation was hypothesized to go through a double-displacement mechanism formed by a glycosylation step and a cyclization step. During the glycosylation step, E270 protonates the O2 of the α-D-fructofuranosyl group in the subsite –1 (–1 sugar), E291 attacks the anomeric carbon forming a glycosyl-enzyme intermediate (GEI), and a water molecule is released. During the cyclization, activated by a complex torsional mechanism, the O1 of the β -D-fructofuranosyl group in the subsite +1 attacks the anomeric carbon, cleaving the glycosyl-E291 bond and transferring a proton to the E270. Using

hybrid QM/MM metadynamics methods, we demonstrate the energetic accessibility of the glycosylation + cyclization mechanism for the αFFase1-inulobiose complex. Our simulations show a slightly exothermic global reaction ($\Delta G0 = -1.3$ kcal·mol−1) in good agreement with the experimental inulobiose/DFA I resulting ratios (1:8.9). The $\Delta G\ddagger$ and $\Delta G0$ for the glycosylation are 12.3 and –2.8 kcal·mol−1. The rate-limiting step is the cyclization with a $\Delta G\ddagger$ = 15.3 kcal·mol−1. Our study shows that the –1 sugar follows the E5 → E5/4T5 → E3 and E3 → 4E → 4E conformational pathways. Further analysis of the cyclization simulation shows the role of E85, K147, and N226 stabilizing the rotation of the +1 sugar and facilitating the attack of the O1' to the anomeric carbon. Our experiments with the N226A mutant of the αFFase1 confirmed the assistant role of N226 during the synthase activity, while irrelevant during the hydrolysis.

Poster #742   **online**

Calculating Mössbauer Parameters of Iron Centers in Macromolecules with Density Functional Theory

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57Fe-Mössbauer spectroscopy is an ideal tool to study the electronic and dynamic properties of iron centers in proteins [1]. To predict Mössbauer parameters like the isomer shift δ and the quadrupole splitting ΔEQ of iron centers in proteins and/or complex molecules density functional theory (DFT) calibrations are necessary [2]. We have found that different versions of the public domain software package ORCA [3] gives different results if the same calibration parameters for calculating the isomer shift are used. However, the calibrations can give a good estimation of the parameters if identical basis set for the calibrations are used. Our approach uses an individual calibration for each oxidation state of iron to receive the best prediction of the experimental observables δ and ΔEQ possible.

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Poster #743 online

Vibrational Properties and Protonation States of the [2Fe-2S] Cluster of Apd1 Protein and its Ligands

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Iron sulfur [Fe-S] clusters play an important role for the essential processes of life [1]. The actin patches distal 1 (Apd1) protein is found in bacteria, plants, fungi, and unicellular pathogenic eukaryotes but not in Metazoa. It harbors a Rieske like [2Fe-2S] cluster coordinated by two cysteine and two histidine residues [3]. Depending on the pH the histidine can be protonated or deprotonated which leads to a pronounced change of the electronic properties of the histidine-coordinated iron. Nuclear inelastic scattering (NIS) was used to investigate the pH dependence of the vibrational properties of the [2Fe 2S] cluster. To analyze the data, we performed molecular mechanic (MM) and density functional theory (DFT) calculations on a structural model predicted by AlphaFold [2, 4], as well as on yet unpublished crystal structure data of Apd1 from Saccharomyces cerevisiae.

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Poster #766   **on-site**

V-Nitrogenase Reduction of Carbon Monoxide: A Multiscale Computational Investigation

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Nitrogenases are enzymatic complexes that play a crucial role in the reduction of atmospheric nitrogen (N2) into bioavailable ammonia (NH3), thereby facilitating the nitrogen cycle and supporting life on Earth. Their ability to reduce the stable N2 triple bond under ambient conditions distinguishes them from the industrial Haber-Bosch process, which operates at high temperature and pressure. Nitrogenases can be divided into three main classes based on the identity of the heteroatom in their active site cofactor: molybdenum nitrogenase (Mo-nitrogenase), vanadium nitrogenase (V-nitrogenase), and iron-only nitrogenase (Fe-nitrogenase). Each of these classes exhibits distinct catalytic activities and functional characteristics. Mo- nitrogenase, being the most active and extensively studied among the three classes, has provided valuable insights into the nitrogen-fixation process. However, recent attention has shifted towards V-nitrogenase due to its remarkable ability to bind carbon monoxide (CO) in its resting state and reduce CO predominantly to ethylene. The recent availability of high-resolution X-ray structures of V-nitrogenase provides an excellent starting point for computational investigations. By employing computational modeling and Quantum Mechanical/Molecular Mechanical (QM/MM) studies, we aim to unravel the unique catalytic activity of vanadium nitrogenase in contrast to molybdenum nitrogenase.The Broken Symmetry approach, pioneered by Noodelman, is utilized to investigate the electronic structure of active sites featuring exotic metal cluster. This research aims to provide an atomistic understanding of the CO reduction process. Such insights hold immense biotechnological potential, particularly in the production of biofuels.

Poster #768   **online**

Improving MD Performance on HPC Clusters Through In-Depth Hardware Knowledge and Advanced Program Usage

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Most modern MD simulation programs run out of the box on HPC clusters and yield reasonable performance results. To shed some light on the backgrounds of optimized performance, we present three case studies from user support. First, we present a reduction of hardware costs by 2/3: An REMD simulation with GROMACS reached 124 ns/day for 26 replicas on 12 dual-socket Intel Ice Lake. We were able to port this simulation to eight NVIDIA A40 GPUs while retaining a performance of 120.6 ns/day. Since the number of replicas is not a multiple of eight, porting required assignment of PP- and PME- tasks to the GPUs by hand. The second case is about calling the GROMACS runtime correctly to obtain a performance gain, especially when dealing with a large simulation system of 2,600,000 atoms and a multiple GPU-setup. Starting from a performance of 11.8 ns/day on eight NVIDIA A40 GPUs, we nearly quadrupled performance to 20 ns/day on four A40 GPUs. Thus, about twice the performance on half of the resources by setting environment variables for improved GPU communication and adjusting runtime parameters. Another proof of in-depth hardware knowledge is represented by our third case where ORCA underperformed on our high throughput cluster: A single numerical calculation of molecular frequencies took 76.4 hours to finish. Multiple setups on various CPU architectures followed by detailed examinations sped up this simulation to 11 hours on the same node; the statically linked OpenBLAS library falsely detected the underlying hardware.