Oral #16 **on-site**

Towards Cell-Scale Molecular Simulations

Presenting author: **Gerhard Hummer**

Max Planck Institute for Biophysics, Department of Theoretical Biophysics, Frankfurt/Main, Germany

Co-author/s: Marc Siggel, Sören von Bülow

Living organisms constantly remodel the structure, topology, composition, and chemistry of their lipid membranes using elaborate protein machineries. Molecular simulations of membrane remodeling processes remain challenging because of large spatial scales, long time scales as a result of high energetic barriers and the slow intrinsic dynamics of membranes, and the incompatibilities of changes in membrane topology with periodic boundary conditions. In my presentation, I will present results of our computational and theoretical studies of membrane dynamics and remodeling in autophagy, nuclear transport, infection, and drug delivery. I will highlight our attempts at addressing challenges, for instance by using tension and membrane leaflet asymmetry to modulate the membrane insertion propensity and the energetics of membrane shape changes.

Oral #40 **on-site**

Mechanistic Insight into Seipin's Activity During Initial Stages of Lipid Droplet Formation

Presenting author: **Xavier Prasanna Anthony Raj**

University of Helsinki, Department of Physics, Biological Physics and Soft Matter Group, Helsinki, Finland

Co-author/s: Veijo Salo, Shiqian Li

Lipid droplets (LDs) are ubiquitous, sub-cellular organelles that serve as lipid reservoirs for membrane synthesis and energy metabolism. Abnormalities in lipid homeostasis is associated with metabolic disorders such as obesity and insulin resistance. Understanding the mechanism of LD metabolism has significant implications in treatement of these disorders. A key player involved in LD formation is seipin, an endoplasmic reticulum (ER) transmembrane protein. LD synthesis occurs through aggregation of neutral lipids such as triacylgycerols (TAGs) and sterol esters (SE) within ER. Seipin has been shown to localise at the ER-LD contact interface. In the absence of seipin, cells generate irregular-sized LDs and exhibit functional defects in the ER-LD contacts. However, the molecular mechanism by which seipin regulates LD formation and stability is largely unknown. In this study, we use multi-scale molecular dynamics simulations along with cell biology experiments to explore the mechanistic and functional role of seipin in initiation and formation of LDs. Our study shows that seipin promotes TAG nanoclustering at concentrations that by itself is insufficient for TAGs to cluster within the ER membrane. Seipin sequesters TAGs from the ER bilayer into its lumen via the luminal hydrophobic helices of the protomers which arranged as a ring and embedded within the bilayer. We identified S166 as a critical residue in the luminal helix which serves as a nucleation site for TAG aggregation. Mutating this residue was shown to decrease TAG nucleation within seipin lumen and subsequently compromise seipin-mediated TAG sequesteration and LD formation. Our findings provide molecular details of the mechanism by which seipin mediates LD formation.

Oral #103 **online**

Mechanistic Insights into the Differential Dynamics of SARS-CoV-2 Variants of Concern (VOC)

Presenting author: **Nabanita Mandal**

National Institute of Technology, Department of Biotechnology, Computational Biophysics, Warangal, India

Co-author/s: Aditya K. Padhi, Soumya Lipsa Rath

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has affected the lives and livelihood of millions of individuals around the world. It has mutated several times after its first inception, with an estimated two mutations occurring every month. Although we have been successful in developing vaccines against the virus, emergence of variants has enabled it to escape therapy. Few of the generated variants are also reported to be more infectious than the wild-type (WT). In this study, we analyse the attributes of all RBD/ACE2 complexes for the reported VOCs, namely, Alpha, Beta, Gamma, and Delta through computer simulations. Results indicate differences in orientation and binding energies of the VOCs from the WT. Overall, it was observed that electrostatic interactions play a major role in the binding of the complexes. Detailed residue level energetics revealed that the most prominent changes in interaction energies were seen particularly at the mutated residues which were present at RBD/ACE2 interface. We found that the Delta variant is one of the most tightly bound variants of SARS-CoV-2 with dynamics similar to WT. High binding affinity of RBD towards ACE2 is indicative of an increase in the viral transmission and infectivity. The details presented in our study would prove extremely useful for the design and development of effective therapeutic strategies for the emerging variants of the virus.

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Oral #180 **on-site**

Thermodynamic Driving Forces of Guest Confinement in a Photoswitchable Cage

Presenting author: **Anna Selina Juber**

Ruhr University Bochum, Department of Theoretical Chemistry, Biomolecular Simulation Group, Bochum, Germany

Co-author/s: Sebastian Wingbermuehle, Patrick Nuernberger, Guido H. Clever, Lars V. Schäfer

Photoswitchable cages that confine small guest molecules inside their cavities offer a way to control the binding/unbinding process through irradiation with light of different wavelengths. However, a detailed characterization of the structural and thermodynamic consequences of photoswitching is very challenging to obtain by experiment alone. Thus, all-atom molecular dynamics (MD) simulations were carried out to gain insight into the relationship between structure and binding affinity. Binding free energies of the B12F12 guest were obtained for all photochemically accessible forms of a photoswitchable dithienylethene (DTE) based coordination cage. The MD simulations show that successive photo-induced closure of the four individual DTE ligands that form the cage gradually decreases the binding affinity. Closure of the first ligand already significantly lowers the unbinding barrier and the binding free energy, and therefore favours guest unbinding both kinetically and thermodynamically. Analysis of the different enthalpy contributions to the free energy shows that binding is enthalpically unfavourable and thus an entropy-driven process, in agreement with experimental data. Dissecting the enthalpy into the contributions from electrostatic, van der Waals, and bonded interactions in the force field shows that the unfavourable binding enthalpy is due to the bonded interactions being more favourable in the dissociated state, suggesting the presence of structural strain in the bound complex. Thus, the simulations provide microscopic explanations for the experimental findings and open a possible route towards the targeted design of switchable nanocontainers with modified binding properties.

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Oral #263 **on-site**

Does the Inclusion of Polarisability Lead to a Better Modelling of Peptide Aggregation?

Presenting author: **Batuhan Kav**

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

Co-author/s: Birgit Strodel

Exclusion of explicit polarisability from the classical molecular dynamics (MD) force fields has been discussed since the dawn of MD simulations as a field. Although many models to treat electronic polarisability have been proposed, until recently it has not been possible to generate MD trajectories long enough to assess the effect of electronic polarisability in the context of protein aggregation. The Aβ16-22 fragment of the Aβ42 protein, whose aggregation into senile plaques has been considered as a hallmark of the Alzheimer's disease, is a popular system to study the aggregation behaviour of peptides. In this work, we perform μs-long MD simulations of the Aβ16-22 monomers and dimers using the CHARMM-Drude polarisable force field. We quantify the structural preferences of this peptide as well as its interactions with water and monovalent ions. We further compute kinetic transition networks for Aβ16-22 dimerisation to understand the general aggregation behaviour. Our results show that compared to the state-of-the-art CHARMM36m non-polarisable force field, the CHARMM-Drude force field causes the Aβ16-22 peptide to have an overly strong tendency to bind to the monovalent ions, to form fewer hydrogen bonds with water and less β-sheets. We discuss the consequences of these structural differences in the context of peptide aggregation.

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Oral #328 **on-site**

Constant pH Molecular Dynamics in GROMACS using Lambda Dynamics and the Fast Multipole Method

Presenting author: **Eliane Briand**

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

The residue protonation state of biomolecules is usually treated as fixed in molecular dynamics (MD) simulations: this is equivalent to a time-varying pH. Numerous approaches are found in the literature to obtain a more realistic constant pH by dynamically altering protonation, however these tend to be too slow or too complicated for routine use. Building upon the established lambda dynamics method with Hamiltonian interpolation, we aim to make constant pH MD (CPH-MD) accessible to the non-expert by an intuitive interface, a user-oriented documentation, and a performance high enough for use beyond small proteins through FMM electrostatics. To illustrate practical usages of our implementation as well as sketch an accuracy profile, we present titration results for small histidine and glutamate-containing peptides with pKa shifted by their proximate environment, as well as the usual CPH-MD benchmark protein lysozyme.

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Oral #339 **on-site**

DNA Opening During Transcription Initiation by RNA Polymerase II in Atomic Detail

Presenting author: **Jeremy Lapierre**

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Co-author/s: Jochen S. Hub

RNA polymerase II (RNAP II) is a macro-molecular complex that synthesizes RNA by reading the DNA code, a process called transcription. During transcription initiation, RNAP II opens the double-stranded DNA to expose the DNA template to the active site. The molecular interactions driving and controlling the DNA opening are not well understood. We used all-atom molecular dynamics (MD) simulations to obtain a continuous atomistic pathway for the DNA opening process in human RNAP II, starting from the conformation with double-stranded DNA up to the the conformation with an open DNA bubble loaded into the active site. To achieve such large-scale and highly nonlinear transition, we steered the MD simulations along a combination of collective variables involving a guided DNA rotation and a set of path collective variables. The simulations reveal extensive interactions of the DNA with three protein loops near the active site, namely the rudder, fork loop 1, and fork loop 2. According to the simulations, these DNA-protein interactions support DNA opening by attacking Watson-Crick hydrogen bonds, and they stabilize the open DNA bubble by the formation of a wide set of DNA-protein salt bridges.

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Oral #340 **online**

Manipulation of a Cryptic Site on DHFR to Combat Trimethoprim Resistance in *E. coli*

Presenting author: **Ebru Çetin**

Sabanci University, Material Science and Nano Engineering, MIDTSLAB, Istanbul, Turkey

Co-author/s: Hanife Pekel, Özge Şensoy, Ali Rana Atilgan, Canan Atilgan

Antibiotic resistance has mainly emerged as a result of targeting the orthosteric ligand binding site of bacterial proteins by drugs having similar scaffolds. Moreover, antibiotic discovery studies have focused on wild type proteins; however, bacteria adopt various mutations to survive in their challenging environment [1]. Although such studies provide valuable information on the mutations preferred by resistant bacteria, they are far from providing a mechanistic insight into such preferences, which hampers design of effective therapeutics in a systematic manner. Therefore, in this study, we are motivated to develop a novel computational strategy which can be used to identify cryptic sites and candidate molecules that can prevent/alleviate resistance. Towards this end, we used dihydrofolate reductase (DHFR) from E. coli as our target system and performed molecular dynamics (MD) simulations using wild type and the most resistant mutant form, L28R, of DHFR [2,3] to reveal changes that occur in both local and global properties of these proteins. Here, we first discuss the discovery of a potential cryptic site, which is 28 Å away from the binding pocket, by scrutinizing the changes in the hydrogen bond dynamics in MD simulations and supported by shifts in electrostatic potential distributions. We also then present an extensive drug repurposing study that targets the potential cryptic site via sitemap analysis, pharmacophore design, and virtual screening by exploiting NPC drug database, followed by MD simulations of selected candidates. We find that the drug proglumetacin displays a good binding behavior at the cryptic site of the wild-type. It also displays similar effects to trimethoprim at GH loop and orthosteric site.

[1] Toprak et al. Nature Protocols 2013, 8 (3), 555-567.

[2] Abdizadeh et al. Physical Chemistry Chemical Physics 2017, 19 (18), 11416-11428.

[3] Tamer et al. Molecular Biology and Evolution 2019, 36 (7), 1533-1550.

[4] Manna et al. Nature Communications 2021, 12 (1), 2949

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Oral #351 **on-site**

Constant pH MD in GROMACS

Presenting author: **Pavel Buslaev**

University of Jyväskylä, Department of Chemistry, Computational Chemistry of Biomolecules Research Group, Jyväskylä, Finland

Co-author/s: Noora Aho, Anton Jansen, Paul Bauer, Gerrit Groenhof, Berk Hess

Molecular dynamics (MD) computer simulations allow to extract important information about the dynamical properties of biomolecules hardly accessible with other techniques. The simulations are usually performed at the pressure and temperature used in the experimental studies of the investigated system. While the proton concentration (pH) is an equally important parameter in experiments, it is rarely accounted for in simulations due to various methodological issues. For instance, λ-dynamics based constant pH MD was implemented in a fork of GROMACS release 3.3, but due to poor scaling of the code with respect to the number of titratable groups, the uptake was limited. We have overcome this limitation by implementing an alternative scheme of Hamiltonian interpolation, the cornerstone of λ-dynamics. The performance of this algorithm does not depend on the number of titratable groups and is comparable with the performance of normal GROMACS runs. After sharing the main features of our implementation, I will focus on the main problems we encountered while testing the code and their solutions. One of the key problems is the accuracy of the force field for constant pH MD. Due to a significant correlation between the side chain rotamers and proton affinity, in combination with a high barrier for rotamer transitions, the protonation dynamics can converge poorly. To overcome this limitation for the CHARMM36 force field, we decreased the dihedral barriers. We confirmed that with these force field modifications, we can sufficiently increase the sampling of the protonation states without compromising the configurational sampling. Next, I will discuss our protocols for consistently generating parameters for constant pH simulations and preparing systems for such simulations with GROMACS.

Oral #380 **online**

Identification of Gating Sensitive Residues in TREK-2

Presenting author: **Chun Kei Lam**

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Co-author/s: Bert L. de Groot

TREK-2, a two-pore domain potassium (K2P) channel, is known to respond to a wide range of stimuli, such as pH, membrane tension, and binding of small ligands. Moreover, an "up" and a "down" x-ray crystallographic conformations, where the main difference lies in the position and orientation of the transmembrane helix M4, have been resolved and it has been shown that the "up" conformation has higher ion conductance. However, molecular explanations for gating mechanisms and whether transitions between these two conformations play an important role in gating remain elusive. We use molecular dynamics (MD) simulations and free energy calculations to predict how the conformational equilibrium between the "up" and the "down" conformations of TREK-2 is shifted by mutation. We identify several mutants that exhibit a considerable shift towards the "up" conformation. Furthermore, most of the conformational shifts due to mutation can be attributed to either strengthened steric clash or weakened favorable interactions in the cytoplasmic part of M2, M3, and M4. These findings shed light on the molecular roles of the identified gating sensitive residues in governing transitions between the two conformations, which potentially serve as a gating mechanism of TREK-1 and TREK-2 under different physiological conditions.

Oral #381 **on-site**

Identifiying Collective Motion in Proteins - Divide and Conquer the Feature Space

Presenting author: **Georg Diez**

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Co-author/s: Daniel Nagel, Gerhard Stock

Molecular dynamic simulations provide an effective tool for a deeper understanding of proteins and their functioning. In order to shed light on the underlying mechanisms of processes, one typically models the dynamics using some key internal coordinates (or features) which capture the most important conformational changes of the protein. However, one often ends up in a high-dimensional feature space which hampers a straightforward interpretation of the typically very complex dynamics. Adopting the Leiden community detection algorithm [1], we present an effective and scalable approach to divide the feature space into subsets describing collective motion. By applying this approach to the functional dynamics of T4 lysozyme, the allosteric transition of PDZ2 domain and the folding of villin headpiece, we show that it allows to identify and discard uncorrelated motion and noise. Moreover, it provides an effective dimensionality reduction scheme by extracting the key features, and leads to a detailed understanding of the underlying mechanisms.

[1] Traag et al., "From Louvain to Leiden: guaranteeing well-connected communities", Sci. Rep., 2019

Oral #414 **on-site**

A Cooperative Knock-On Mechanism Underpins Ca2+-Selective Cation Permeation in TRPV Channels

Presenting author: **Callum M. Ives**

University of Dundee, Division of Computational Biology, School of Life Sciences, Dundee, United Kingdom

Co-author/s: Neil J. Thomson, Ulrich Zachariae

The selective exchange of ions across cellular membranes is a vital biological process. Due to the significance of Ca2+ in a broad array of cellular processes, strict concentration gradients are maintained across the plasma and organelle membranes. Therefore, Ca2+ signalling relies on permeation through selective ion channels that control the flux of Ca2+ ions. A key family of Ca2+-permeable membrane channels are the polymodal signal-detecting TRPV ion channels, a subfamily of the Transient Receptor Potential (TRP) channels. Although most members of this family permeate cations non-selectively, TRPV5 and TRPV6 are unique due to their strong Ca2+-selectivity. Through the use of atomistic molecular dynamics simulations we probed the question of how TRPV5 and TRPV6 show such Ca2+-selectivity, despite other TRPV channels conducting a wider spectrum of cations. We present simulations demonstrating continuous permeation of both Na+ and Ca2+ cations through both Ca2+-selective and non-selective TRPV channels. Our results show that cation permeation in Ca2+-selective TRPV channels occurs by a knock-on mechanism between three binding sites; each binding site exhibiting preferential binding of Ca2+ over Na+. Moreover, our results quantify the degree of cooperativity in the knock-on mechanism using a novel application of mutual information, termed state specific information. In contrast, simulations of non-selective TRPV channels showed that cation permeation occurred between only two binding sites and with a lower level of knock-on cooperativity. We conclude that the presence or absence of a third ion binding site in the channel underpins the degree of Ca2+-selectivity.

Oral #432 **on-site**

A New Measure for Contact Maps

Presenting author: **Christian Faber**

Research Center Jülich, Jülich Supercomputing Centre, NIC research group Computational Structural Biology, Jülich, Germany

Co-author/s: Alexander Schug

Predicting the structure of biological molecules such as proteins and RNA has become an exciting challenge in recent years.

By utilizing the nucleotide sequence of RNA molecules, simulations of their 3d structure can be created. Another approach is the analysis of multiple sequence alignments of homologous molecules through the use of statistical methods[1]. For instance, Direct Coupling Analysis (DCA) is able to detect direct correlations between two different positions in the primary structure using a Potts model. From that we obtain a possible contact map that we can use as an input constraint for folding programs. To evaluate such co-evolutionary and other, e.g. machine learning, methods, the Positive Predicted Value (PPV) can be calculated as a measure.

Unfortunately, recent studies[2] have shown that despite an enormous increase in PPV, the predicted folded structures hardly improved. Here we present a new measure which weights every contact with a Gaussian distribution. As a result the impact of new contacts, found in already detected clusters, decreases. We also show the dependence of this new measure on the 3d structure prediction.

[1] Weigt, M., White, R. A., Szurmant, H., Hoch, J. A., & Hwa, T., Proceedings of the National Academy of Sciences, 106(1), 67-72 (2009).

[2] Zerihun, M.B., Pucci, F., Schug, A., Nucleic Acids Research, 49(22), 12661–12672 (2021).

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Oral #441 **on-site**

Structural Basis of the Transmembrane Domain of the Yeast Mitofusin Fzo1

Presenting author: **Raphaëlle Versini**

Sorbonne University, PSL Research University, University of Paris, Institute of Physical and Chemical Biology - Edmond de Rothschild Foundation, Biomolecules Laboratory (LBM), Laboratory of Theoretical Biochemistry (LBT, Paris, France)

Co-author/s: Antoine Taly, Patrick Fuchs

Outer mitochondrial membrane (OMM) fusion is an important process for the cell and organism survival, as its dysfunction is often linked to neurodegenerative diseases. The OMM fusion is mediated by members of the dynamin-related protein (DRP) family, named mitofusins. Fzo1, the only mitofusin homologue of the yeast Saccharomyces cerevisiae and embedded in the OMM, was modeled in literature by homology with the mitofusin related bacterial dynamin-like protein (BDLP) as template. However BDLP does not possess any transmembrane part. Thus, the structure of the Fzo1 transmembrane domain, made of two putative helices TM1 and TM2, had to be determined using ab initio methods. One study in literature predicted the structure of Fzo1 transmembrane domain using the webserver PREDIMMER.

Furthermore, TM1 has a lysine (Lys716) located inside the membrane which could either be protonated or unprotonated. The first construction assumed this lysine to be neutral.

Coarse-grained representations, with the MARTINI force field, are used in order to sample a massive amount of TM1/TM2 possible associations. However, MARTINI2 has been shown to over-aggregate proteins, an issue that seems to be resolved in the latest version of the force field MARTINI3.

In this work, we will compare results from MARTINI2 and MARTINI3, as well as the different protonation states of the TM1.

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Oral #449 **on-site**

Towards Quantitatively Accurate Neural Network CG Force-fields

Presenting author: **Aleksander Durumeric**

Free University Berlin, Mathematics, Berlin, Germany

Co-author/s: Frank Noe, Cecilia Clementi

Machine learning (ML) based force-fields have transformed atomistic molecular dynamics simulations; however, their coarse-grained (CG) counterparts have lagged behind in terms of accuracy. In this talk we describe recent progress towards ML-based quantitatively accurate CG models of a single protein, including both modified parameterization and error characterization techniques. Together, these approaches provide initial evidence that CG models may eventually reach the accuracy of their atomistic counterparts.

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Oral #486 **on-site**

Local Mode Softening versus Hardening Underpins Specific Allosteric Responses

Presenting author: **Maximilian Vossel**

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

Co-author/s: Aljaž Godec

Allostery – the ability of proteins to exhibit specific structural responses to the binding of ligands at spatially remote sites – enables control over protein function. Allosteric modulation of conformations is a promising new avenue for drug discovery, and is nowadays employed in the design of mechanical metamaterials. However, allostery has proven much harder to predict than to design. Functional allosteric motions are specific, non-linear, and require concerted rearrangements. A general method for identifying allosteric source-target pairs that carry a targeted response remains elusive. Focusing on elastic network models, we here establish physical principles that govern the directional, i.e. source-to-target, allosteric communication. Local "hardening" versus "softening" of eigenmodes of the Hessian matrix of the network is shown to identify source and target sites, but alone does not encode a specific allosteric response. The latter is typically non-linear and involves an interplay of many modes. An efficient computational method for determining said non-linear response is presented that identifies and ranks candidate source sites for a specific response of a known target. These principles are corroborated by 30 trained networks and 14 allosteric proteins. Our results provide a physical basis for allosteric drug design.

Oral #501 **online**

Peptide Deformylase as a Probe of Long-Range Allostery Through the Ribosomal Protein uL22

Presenting author: **Hugo McGrath**

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

Co-author/s: Michaela Černeková, Michal H. Kolář

Proteosynthesis on ribosomes is regulated on many levels. The regulatory mechanisms may involve conformational changes of the ribosome induced by external factors possibly transferred over large distances. The principles of this allosteric communication between distant ribosome parts are not fully understood yet. Here we investigate peptide deformylase, an enzyme that binds to the ribosome surface near the ribosomal protein uL22 during translation and modifies the emerging nascent chain, to understand how conformational motion of the ribosome is affected by external factors.

We have performed both equilibrium and non-equilibrium all-atom molecular dynamics simulations of the entire ribosome and analyzed these simulations using Functional mode analysis, a form of supervised learning. The results indicate conformational changes of the ribosomal protein uL22 inside the ribosomal exit tunnel upon deformylase binding suggesting a possible effect of the deformylase on the nascent peptide transport through the tunnel. Moreover, the simulations provide an atomistic picture of the deformylase motion on the ribosome surface, explaining some details about the enzymatic reaction.

Oral #506 **on-site**

Thiol-Disulfide Exchange Reactions Using an Artificial Neural Network Corrected DFTB/MM Methodology

Presenting author: **Claudia Leticia Gomez Flores**

Karlsruhe Institute of Technology, Institute of Physical Chemistry, Theoretical Chemical Biology, Karlsruhe, Germany

Co-author/s: Denis Maag, Tomáš Kubař and Marcus Elstner

Semi-empirical methods like DFTB allow extensive phase space sampling, making it possible to generate free-energy surfaces of complex reactions in condensed-phase environments with a low computational cost. However, these savings in computational costs can come at the expense of lower accuracy. Our system of interest is the thiol-disulfide exchange reaction, a nucleophilic substitution that occurs in a large class of proteins, for which proper description requires high-level ab intio methods.

To learn and correct the DFTB miscalculations against ab initio methods was the motivation of our project. To achieve this, we used a Behler–Parrinello-type Neural Network that learns the energy value differences between the ab initio quantum chemical potential and DFTB for a given molecular structure. The implementation of the machine learning energy correction and force calculation into DFTB+ allowed to perform quantum mechanical simulations with both Coupled Cluster and B3LYP accuracy, with comparable scaling of semi-empirical methods.

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Oral #509 **on-site**

Avidity of the Malaria Adhesin VAR2CSA is Mechano-Controlled by Exposure of a Second Cryptic CSA Sugar Binding Site

Presenting author: **Nicholas Michelarakis**

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

Co-author/s: Nicholas Michelarakis, Rita Rössner, Frauke Gräter , Camilo Aponte-Santamaría

Plasmodium falciparum (Pf) is responsible for the most lethal form of malaria. In the bloodstream, Pf infects erythrocytes increasing their adhesivity to different organs to avoid the immune clearance response in the spleen. VAR2CSA is the adhesin protein expressed by the parasite at the membrane of the infected erythrocytes for attachment on the placenta, leading to pregnancy-associated malaria. VAR2CSA is a large 350 kDa multidomain protein composed of nine extracellular domains, a single spanning helical transmembrane segment, and an intracellular domain. Chondroitin Sulphate A (CSA), located in the intervillous space of the placenta, serves as the substrate and anchor point of VAR2CSA. Due to its adhesive function, VAR2CSA is a target of vaccines against placental-malaria. Shear flow, as the one occurring in blood, has been shown to enhance VAR2CSA adhesion on the CSA-matrix. However, the underlying molecular mechanism by which this mechanical mode of perturbation influences the adhesivity of this protein still remains elusive. Here, we shed light on this question through the use of million-atoms equilibrium and force-probe molecular dynamic simulations, with a cumulative sampling time of more than 2.5 µs. We subjected the VAR2CSA protein-CSA sugar complex to a force mimicking the elongational tension on this system arising from the shear of the flowing blood. We show that upon this force exertion, the CSA sugar chain dissociates from the protein, but before that, the VAR2CSA protein undergoes a large opening conformational transition, exposing a secondary CSA binding site. Molecular docking followed by extensive equilibrium molecular dynamics relaxation suggest that a dodecameric CSA molecule can stably accomodate to the force-exposed binding site. Our results thus suggest that mechanical force increases the avidity of VAR2CSA by uncovering a secondary cryptic CSA binding site. The mechanism provided here paves the way to understanding the molecular mechanism governing the shear enhanced VAR2CSA-CSA interaction highlighting the mechano-activated protein-sugar avity employed by Pf during malaria-infected erythrocyte adhesion.

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Oral #520 **on-site**

Membrane Curvature Induced Lipid Sorting in Coarse-Grained Simulations

Presenting author: **Melanie König**

University of Groningen, Groningen Biomolecular Sciences and Biotechnology Institute, Molecular Dynamics Group, Groningen, The Netherlands

Co-author/s: Reinier de Vries, Weria Pezeshkian, Siewert-Jan Marrink

Generation, modulation, and maintenance of membrane curvature is an important property of all biological membranes. Many organelles rely on highly curved vesicular and tubular structures, including the membranes of the peripheral endoplasmic reticulum and the inner membranes of mitochondria. Both proteins and lipids contribute to inducing and maintaining a variety of membrane shapes, therefore their spatial distribution is coupled to the membrane curvature. While the ability of membrane-bound proteins to generate and sense curvature has been extensively studied, the coupling between lateral segregation of lipids and membrane curvature is less understood.

Using molecular dynamics simulations at near-atomic resolution, we systematically studied the sorting of various lipid types in increasingly complex membranes. Different degrees of curvature were generated using a wall to preserve the membrane shape. For simple lipid mixtures, the lipid distribution matches the lipid shape with the membrane curvature e.g., cone shaped cardiolipin segregates to negatively curved membrane regions. Additionally, we have shown that the extent of sorting is strongly influenced by the magnitude of curvature, lipid ratio, membrane asymmetry and ion concentration, which are important factors in controlling biological membranes. In more complex lipid mixtures, curvature induced lipid sorting is less pronounced compared to other effects like phase separation. However, the interplay between both effects might be important for many biological functions involving shape remodeling processes like endocytosis and exocytosis.

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Oral #526 **on-site**

Artificial Intelligence for Molecular Mechanism Discovery

Presenting author: **Hendrik Jung**

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Co-author/s: Roberto Covino, A. Arjun, Christian Leitold, Peter G. Bolhuis, Christoph Dellago, Gerhard Hummer

We develop a machine learning algorithm to extract the mechanism of transition between metastable states from molecular dynamics simulations. Our algorithm combines transition path sampling (TPS), deep learning, and statistical inference to simulate the dynamics of complex molecular reorganizations while simultaneously learning how to predict their outcome. We iteratively train a deep learning model on the outcomes of the shooting moves used in TPS. While learning to predict the transition dynamics the artificial intelligence (AI) gradually reveals the underlying mechanism of the transition dynamics, and at the same time increases the efficiency of the rare-event sampling. Additionally, the AI can simultaneously learn from and guide multiple TPS simulations, becoming increasingly effective in learning the transition dynamics with increasing degree of parallelization. In a second step, we then distill the knowledge about the reaction encoded in the deep learning model into a reduced mathematical model. The reduced model describes only the most concise features of the transition ensemble in a human-understandable manner.

We apply the algorithm to molecular systems ranging from ion dissociation in aqueous solution to the oligomerization of a transmembrane alpha helix involved in membrane sensing. In all cases the AI is able to accurately predict the transition dynamics and the reduced mathematical models help illuminate the succinct features of the studied mechanisms.

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Oral #527 **on-site**

Anchoring of the SARS CoV-2 Fusion Peptide in Host Membranes

Presenting author: **Stefan Schäfer**

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Like other enveloped viruses, SARS-CoV-2 has to fuse its viral membrane with the host membrane to deliver its genomic RNA into the cytoplasm and to hijack the cellular machinery of the host. To facilitate this membrane fusion, the virus first tethers a membrane anchor — the fusion peptide (FP) — to the host membrane. During this process the FP must perform the balancing act of binding quickly, yet anchoring strongly enough to transmit the force that subsequently pulls virus and host membranes together.

From extensive molecular dynamics simulations, we determined the mechanism of FP binding to human endosome and plasma membranes targeted by SARS-CoV-2. We found that three short helical elements connected by flexible linkers drive the fast insertion of the FP into the membrane interface. These short helical elements can bind independently, yet binding of one likely promotes additional binding of the other two.

To further assess the strength of binding of the identified binding modes, we then subjected the anchored FP to simulated pull force. We showed that the interface-bound FP can withstand mechanical forces of more than 200 pN before detaching from the membrane. These forces substantially exceed those estimated to act during viral fusion. Furthermore, the simulated pulling allowed us to identify a fully conserved disulfide bridge that connects two of the short helices and acts as a force-bearing element. This disulfide bridge redistributes the force load, so that the amphipathic helix is forced to detach with its entire hydrophobic face at once, instead of being lifted out more gently from the end.

We thus gained insight into the attachment of the activated viral membrane fusion machinery to the human host cell, the transmission of force as required for membrane fusion and cell entry, and the forced detachment from the membrane.

Hybrid Workshop, April 8-9, 2022
"COMPUTER SIMULATION AND THEORY OF MACROMOLECULES"

Oral #531 **on-site**

Weighted Ensemble Simulations of SARS-CoV-2 Glycosylated Spike Opening

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To infect cells, the SARS-CoV-2 glycosylated spike protein must bind to the human ACE2 receptor. The spike receptor binding domain transitions from a closed, glycan shielded conformation, to an open, exposed state. Experiments have revealed static conformations of each state, but the dynamic process remains elusive with these methods. Since this process occurs on the seconds timescale, we used an enhanced sampling technique to simulate the pathway. We used the weighted ensemble method, which involves running many short simulations in parallel, splitting those which rarely visit new regions of conformational space, and merging those which sample redundant regions. This focuses computational resources on rare event sampling, allowing multiple orders of magnitude enhancement of sampling. Simulation weights are rigorously tracked, so both thermodynamic and kinetic properties can be characterized. We generated an ensemble of continuous spike opening pathways, elucidating atomic-level details of the mechanism. Most notably, we reveal a glycan gate at position N343, which is responsible for initiating the transition by intercalating underneath and lifting the receptor binding domain into the open state.

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Oral #536 **on-site**

Bending-Torsional Elasticity and Energetics of the Plus-End Microtubule Tip

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Microtubules (MTs), mesoscopic cellular filaments, grow primarily by the addition of GTP-bound tubulin dimers at their dynamic flaring plus-end tips. They operate as chemomechanical energy transducers with stochastic transitions to an astounding shortening motion upon hydrolyzing GTP to GDP. Time-resolved dynamics of the MT tip - a key determinant of this behavior - as a function of nucleotide state, internal lattice strain, and stabilizing lateral interactions have not been fully understood. Here, we use atomistic simulations to study the spontaneous relaxation of complete GTP-MT and GDP-MT tip models from unfavorable straight to relaxed splayed conformations and to comprehensively characterize the elasticity of MT tips. Our simulations reveal the dominance of viscoelastic dynamics of MT protofilaments during the relaxation process, driven by the stored bending-torsional strain and counterbalanced by the inter-protofilament interactions. We show that the post-hydrolysis MT tip is exposed to higher activation energy barriers for straight lattice formation, which translates into its inability to elongate. Our study provides an information-driven Brownian ratchet mechanism for the elastic energy conversion and release by MT tips and offers new insights into the mechanoenzymatics of MTs.