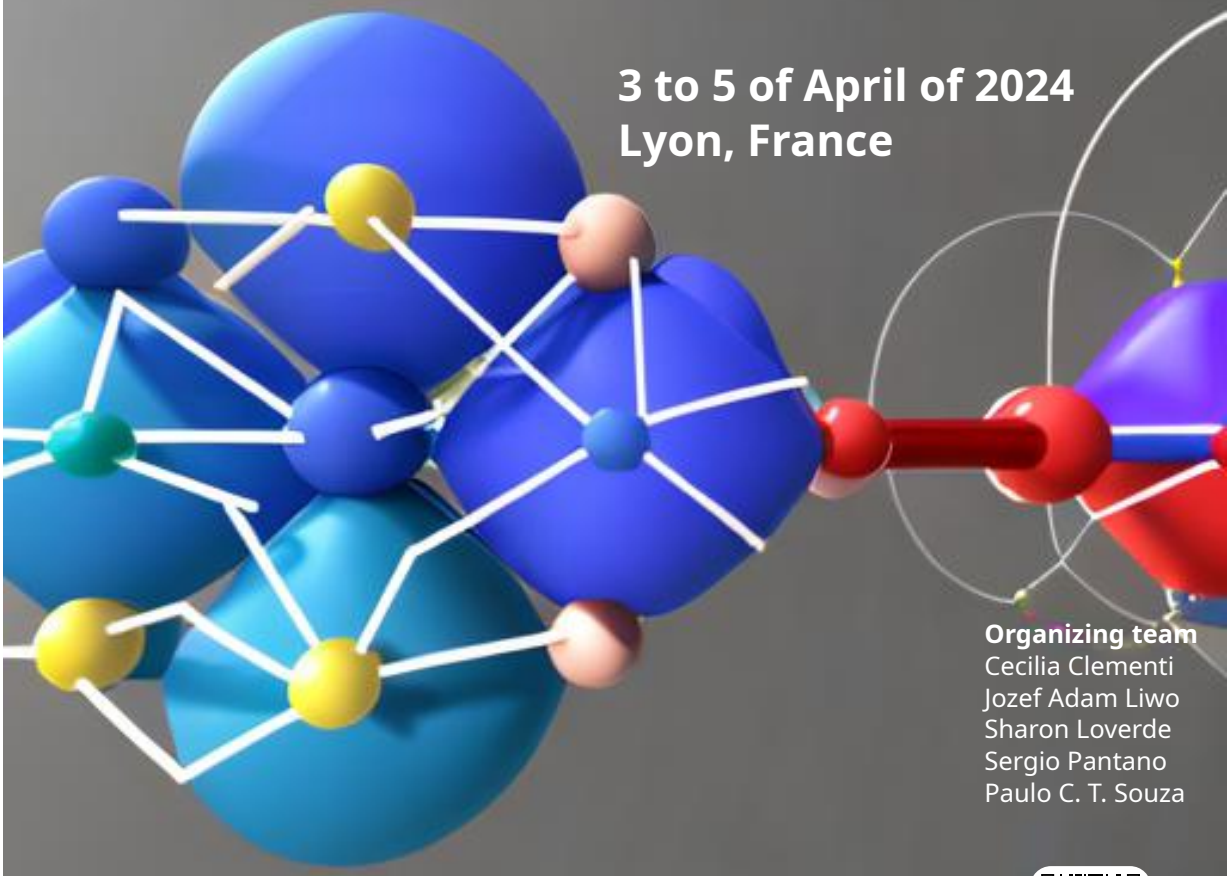
Frontiers of Coarse-Grained Models

CECAM Flagship Workshop



3 to 5 of April of 2024
Lyon, France

Organizing team
Cecilia Clementi
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Sergio Pantano
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From New Developments to Modeling Dynamics, Assemblies, and Macromolecular Machines

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CECAM Flagship Workshop

Frontiers of Coarse-Grained Models:

From New Developments to Modeling Dynamics, Assemblies, and Macromolecular Machines

April 3, 2024 – April 5, 2024

Salle Condorcet, École Normale Supérieure de Lyon
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Organisers

Cecilia Clementi (Freie Universität Berlin)
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Program and Abstracts

Contents

Description

By expanding the boundaries of time and length scales beyond atomistic models, the development of coarse-grained (CG) models has emerged as a vibrant area of research with far-reaching implications for both academia and industry. This workshop aims to bring together active researchers in this field, serving as a catalyst for sharing insights, innovative methodologies, and solutions to overcome scientific and technical obstacles that lie ahead.

Spanning a diverse range of disciplines, from the intricacies of biology and biophysics to the practical applications in (bio)molecular design, this workshop covers a broad spectrum of subjects with special emphasis for coarse-grained models to study conformational dynamics, macromolecular machines and assemblies, in particular proteins, nucleic acids and their interactions with other biomolecules. We will revisit the state of art of CG models that intricately capture the chemical nature of the molecules, employing both top-down and bottom-up approaches. Notably, CG force-fields such as MARTINI, SPICA, and SIRAH are crafted through a top-down methodology using experimental data, while more systematic bottom-up approaches as UNRES, force-matching and iterative Boltzmann Inversion, are designed from atomistic high-resolution models. In addition, we present the most recent developments on structure- and knowledge-based statistical based CG models, with a dedicated session to newly crafted AI-based approaches for CG modeling. We will gather many of the main CG developers world-wide to discuss crucial methodological aspects, enabling us to identify the strengths and weaknesses of different approaches. Fundamental questions will be explored, including the comparative merits of more traditional CG approaches and the potential benefits of incorporating or even replacing them for new AI-based strategies. Our collective inquiry will strive to enhance the transferability of CG models, encompassing aspects such as chemistry, temperature, and pressure, while also seeking to refine the definition of coarse-graining.

Our vision extends beyond fundamental research, as we intend to explore the applicability of CG models in the industry, in particular in the fields of drug, protein and delivery design. Additionally, we will delve into the exciting prospects of mesoscopic simulation methods, with a focus on the time and length scales, system description, and properties that are uniquely accessible through such approaches, including applications to crowded complex bio- chemical environments. By participating in this workshop, researchers will gain invaluable insights into the latest advancements within coarse-grained simulations. Collaboration and networking opportunities will abound, facilitating cross-disciplinary interactions and fostering the potential for groundbreaking discoveries. Let us embark on this journey together, pushing the boundaries of coarse-grained modeling and shaping the future of this vital research domain.

Program

Wednesday April 3rd 2024 – Day 1	
12:15 to 13:45	Registration
13:45 to 14:00	Welcome & Introduction
CG Applications I	
Chair: Sergio Pantano	
14:00 to 14:30	Alessandro Barducci – Modeling biomolecular condensates at multiple resolutions
14:30 to 15:00	Horacio V Guzman – Adsorption-driven deformation and footprints of proteins and RNA on biological and inanimate surface
15:00 to 15:15	Coffee break
15:15 to 15:45	Adolfo Poma Bernaola – GōMartini 3: a computational tool to elucidate conformational changes in protein complexes
15:45 to 16:15	Herre Jelger Risselada – Interfacial recognition of lipid membranes
Company Talks	
Chair: Mateusz Sikora	
16:15 to 16:30	Stephane Redon – Modeling coarse-grained systems with the SAMSON platform
16:30 to 16:45	Reinier Akkermans – Coarse-grained modelling in BIOVIA Materials Studio
16:45 to 17:15	Coffee break
Top-Down CG models I	
Chair: Ralf Everaers	
17:15 to 17:45	Siewert-Jan Marrink – Perspective on simulating whole cells with Martini
17:45 to 18:15	Samuela Pasquali – Development of an RNA coarse-grained model: successes and challenges
18:15 to 18:45	Sergei Grudinin – On the simplification of dynamics in molecular systems
18:45 to 20:00	Poster session & aperitif
Thursday April 4th 2024 – Day 2	
Top-Down CG models II	
Chair: Ralf Everaers	
09:00 to 09:30	Kresten Lindorff-Larsen – Coarse-grained models for multi-domain and disordered proteins
09:30 to 10:00	Wataru Shinoda – Recent development of SPICA force field and its application studies

10:00 to 10:30	Coffee break
Data Driven CG	
Chair: Giorgia Brancolini	
10:30 to 11:00	Dominik Gront – Navigating the Landscape of Coarse-Grained Protein Models
11:00 to 11:30	Aldo Pasos-Trejo – A machine-learned, transferable, bottom-up coarse-grained force field for protein simulation
11:30 to 12:00	Janusz Bujnicki – Coarse-grained modeling of RNA 3D structure and interactions, with restraints derived from experimental data
12:00 to 14:00	Lunch
14:00 to 14:30	Michele Cascella – Mechanisms of self-assembling of non-conventional surfactants by multiscale modelling and data-driven approaches
14:30 to 15:00	Michael Feig – Residue-based coarse-graining of peptides and proteins: From traditional simulations to direct conformational sampling via machine learning
15:00 to 15:15	Coffee break
Bottom up CG Models	
Chair: Adam Liwo	
15:15 to 15:45	Gregory Voth – Ongoing Advances in the Theory and Application of Coarse-graining
15:45 to 16:15	Simón Poblete – Multiscale modeling of RNA inside viruses: bridging levels of resolution using minimal representations
16:15 to 16:45	Adam Sieradzan – UNICORN – UNIfied COarse gRaiNed Model
16:45 to 17:15	Coffee break
17:15 to 17:45	Alexander Lyubartsev – Bottom-up coarse-graining: Theory and selected applications
17:45 to 18:15	Grace Brannigan – From data to information: New approaches for extracting coarse-grained targets from atomistic simulations

CG Applications II	
Chair: Sharon Loverde	
18:15 to 18:45	Zoe Cournia – Using Coarse-Grained simulations to understand self-assembly in biomolecular processes
18:45 to 19:15	Valentina Tozzini – Multi-scaling and coarse graining: a bridge between materials and bio-systems
20:00 to 22:00	Conference Dinner
Friday April 5th 2024 – Day 3	
CG Applications II	
Chair: Sharon Loverde	
09:00 to 09:30	Giulia Rossetti – Membranes' effects on sodium channels: Nav1.7 and pain transmission
09:30 to 10:00	Shachi Gosavi – A method for assessing the structural robustness of proteins and its application to geometrically designed and ML designed proteins
10:00 to 10:30	Coffee break
10:30 to 11:00	Lisbeth Ravnkilde Kjølbye – Martini 3 building blocks for lipid nanoparticle design
11:00 to 11:30	Elisa Frezza – Internal Normal Mode Analysis applied to flexibility, dynamics and conformational changes of biomolecules
Young Researcher Talks	
Chair: Marco Cecchini	
11:30 to 11:45	Fabian Grunewald – Strings to Systems
11:45 to 12:00	Marta Pągielska – Bridging Scales in Biomolecular Research: From All-Atom to Coarse-Grained Simulations of Glycosaminoglycan Interactions
12:00 to 12:15	Carlos Henrique Bezerra da Cruz – Design of antimicrobial peptides self-assembled into virus-like capsids
12:15 to 12:30	Tatiana Morozova – Thermo-responsive polypeptides: insights from polymer physics
12:30 to 12:45	Closing & Departure

Invited Talk Abstracts

IT–1

A machine-learned, transferable, bottom-up coarse-grained force field for protein simulation.

Aldo Pasos-Trejo
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The most popular and universally predictive protein simulation models employ all-atom molecular dynamics (MD), but they come at extreme computational cost. The development of a universal, computationally efficient coarse-grained (CG) model with similar prediction performance has been a long-standing challenge. By combining recent deep learning methods with a large and diverse training set of all-atom protein simulations, we have developed a bottom-up CG force field with chemical transferability, which can be used for extrapolative molecular dynamics on new sequences not used during model parametrization. We have demonstrated that the model successfully predicts folded structures, intermediates, metastable folded and unfolded basins, and the fluctuations of intrinsically disordered proteins while it is several orders of magnitude faster than an all-atom model. This showcases the feasibility of a universal and computationally efficient machine-learned CG model for proteins.

IT–2

A method for assessing the structural robustness of proteins and its application to geometrically designed and ML designed proteins

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Naturally occuring single-domain proteins are usually "reasonably" packed. This means that they are not only stable but also populate few to no intermediates during folding. This cooperative folding may be under evolutionary selection because it reduces aggregation. Such reasonable packing requires (1) a protein structure/backbone/topology that can be packed well given the constraints of the sizes of the amino acids and (2) a specific amino-acid sequence which fits this structure, whose energetics stabilize it and which is foldable to the structure. We recently developed a method which tests the response of protein structures to global packing perturbations by using computational protein folding as a read out. I will outline this method (which uses coarse-grained structure-based models and random permutation of the protein sequence) and illustrate its application to understand the packing of designed proteins.

Adsorption-driven deformation and footprints of proteins and RNA on biological and inanimate surface

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Electrostatic and mechanical interactions are crucial for the assembly, disassembly and stability of nanocarriers immersed in biological environments. At the molecular scale, elucidating the organization and structure of e.g. proteinaceous viral capsids in response to interactions with biological or inanimate (material) substrates is a major challenge in biomacromolecular research. Numerous coarse-grained (CG) and enhance-sampling models have been introduced to alleviate those issues. Those methods are generally known as ¨multiscale¨, which can be useful to represent biological and bio-material systems with less degrees-of-freedom, and hence tackle particular questions about diverse physical phenomenologies, like adsorption, and their derivative mechanical deformation, electrostatic interactions in variational environments (different salinities or pH). In this talk, I will present recent in-house developments of multiscale methods [1-5] for the interfaces between proteins with material surfaces and RNA interacting with proteins/membranes. The first part is an example of the characterization of hydrophobic and hydrophilic interactions through simplified self-assembled bilayers. The second focuses on models that provide deeper electrostatic and mechanical insights of the RNA-capsid shell interaction and assembly process. Aiming to learn from those viruses and use them as guidelines for the next-generation efficient drug nanocarriers.

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Bottom-up coarse-graining: Theory and selected applications

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Molecular simulations of many phenomena related to biomolecular systems, soft matter and nanomaterials requires consideration of length scales above 10 nm and time scales longer than 1 mks, which necessitates the use of coarse-grained (low resolution) models, when each site of the model represents a group of atoms, and the solvent is often omitted. While many of coarse-grained models used in different studies in recent years relay on empirically parametrized interaction potentials, the systematic bottom-up coarse-graining approach is based on determination of coarse-grained potentials from atomistic (high resolution) simulations.

In this presentation a multiscale modeling approach based on the inverse Monte Carlo method is discussed, in which averaged structural properties, such as radial distribution functions (RDF) and distributions of internal degrees of freedom of molecular structure, obtained in high-resolution atomistic simulations, are used to reconstruct effective potentials which reproduce the same structural properties within low-resolution coarse-grained model. The theoretical background of the approach, including statistical-mechanical relationships between ensemble averages and potential parameters are discussed including numerical solution according to the iterative Newton scheme. The method is illustrated by several examples of bottom-up coarse-graining of complex multicomponent macromolecular systems: formation of lipid bilayers and other lipid assemblies; deposition of lipid bilayers on nanoparticles; large-scale coarse-grained models of DNA and nucleosome core particles derived exclusively from atomistic simulations. Finally possibility to formulate coarse-grained models using artificial neural network potentials trained on multiple atomistic simulations is discussed and results of a poof-of-concept model are presented.

IT–5

Coarse-grained modeling of RNA 3D structure and interactions, with restraints derived from experimental data

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Ribonucleic acid (RNA) molecules are master regulators of cells. They play key roles in many molecular processes: transmitting genetic information, sensing cellular signals, relaying responses, and even catalyzing chemical reactions. The function of RNA, especially its ability to interact with other molecules, is encoded in its sequence. To understand how these molecules carry out their biological tasks, we need detailed knowledge of RNA structure, dynamics, and thermodynamics. The latter largely determines how RNA folds and interacts within the cellular environment.

Experimentally determining these properties is challenging. Several computational methods have been developed to model the folding of RNA 3D structures and their interactions, mainly with proteins. However, these computational methods are nearing their limits, especially when the biological implications demand calculations of dynamics beyond a few hundred nanoseconds. For researchers facing such challenges, a more effective approach is to use coarse-grained modeling.

I will present strategies for computational modeling of RNA 3D structures and their interactions with other molecules. These strategies use a suite of methods from my laboratory, based on the SimRNA program. Our methods employ coarse-grained representations of molecules, utilize the Monte Carlo method for sampling conformational space, and use statistical potentials to approximate energy. They also help identify conformations that match biologically relevant structures. Specifically, I will discuss computational methods to determine RNA structure using low-resolution experimental data, such as chemical probing and electron microscopy.

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Coarse-grained models for multi-domain and disordered proteins

Kresten Lindorff-Larsen
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Multi-domain proteins and intrinsically disordered regions are pervasive across proteomes in all kingdoms of life, help shape biological functions, and are involved in numerous diseases. These highly flexible proteins populate a diverse set of transiently formed. Recent developments in protein structure prediction have led to the ability to predict the three-dimensional structures of folded proteins at the proteome scale and have enabled large-scale studies of structure-function relationships. In contrast, knowledge of the conformational properties of these more flexible proteins is scarce. In my talk I will describe how we can use molecular simulations with coarse-grained models to study the relationship between sequence, conformational properties, and functions of disordered and flexible multi-domain proteins.

I will describe how we have used experimental data on more than 100 different proteins to learn a coarse-grained molecular energy function to predict conformational properties of disordered and flexible multi-domain proteins. By optimizing a transferable model, called CALVADOS, we can study the conformational ensemble of these proteins in the absence of experimental data. I will describe the Bayesian formalism we developed to parameterize CALVADOS by targeting experimental data on IDRs and multi-domain proteins, including discussions on how best to compare simulations and experiments.

Development of an RNA coarse-grained model: successes and challenges.

Samuela Pasquali

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RNA molecules are characterized by the existence of a multitude of stable states that result in a frustrated energy landscape, where the observed structures depend sensibly on experimental conditions and can depend on the initial, unfolded, structure.

In order to explore the large conformational transitions leading from one state to another we adopt both atomistic and coarse-grained resolutions and enhanced sampling simulations [1,2].

Our coarse-grained model is developed through a top-down approach in the aim of capturing the main interactions governing RNA behavior: base pairing, both canonical and non-canonical, stacking and electrostatics [3].

The model proved successful in the study of relatively small, but complex, molecules such as G-quadruplexes [4], and it is a useful starting point to couple simulations with experimental data, moving toward integrative modeling [5]. Moreover, given the physical understanding of the interactions is preserved, it is possible to couple the force field with models explicitly accounting for pH and develop a CG constant-pH simulation scheme [6].

Given the high level of detail retained by the model, we encounter a bottleneck in determining all of its parameters. While investigating optimization ML methods based on atomistic simulations, we are confronted with the fact that different RNA atomistic force fields give significantly different results in their exploration of energy landscapes and this raises the question on the grounds on which an RNA CG model can be developed.

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IT–8

From data to information: New approaches for extracting coarse-grained targets from atomistic simulations

Grace Brannigan

IT–9

GōMartini 3: a computational tool to elucidate conformational changes in protein complexes

Adolfo Poma Bernaola

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Molecular dynamics (MD) simulation is a powerful tool for revealing the underlying mechanisms governing protein stability. However, a typical disadvantage of the all-atom MD simulation is the limitation to access characteristic length and time scales associated with conformational changes in large biomolecules (i.e. several nm and μs). In contrast, coarse-grained MD has the advantage of expanding this scales by 1-2 orders of magnitude, reducing the computational cost at the expense of losing information on the specific interactions between atoms. The GōMartini approach [1] circumvents this limitation and latest implementation in Martini 3 force field employs virtual sites near the C-alpha atom positions [2]. This approach requires the determination of a native contact map [3] that includes the most relevant interactions between residues. Here I showcase some of the latest studies involving single-molecule force spectroscopy (SMFS) and molecular simulations such as the mechanostability of neutralizing antibodies against SARS-CoV-2 variants and the stability of a therapeutic protein complex. Through refinement of the interaction between residues at the interface of the protein complex, we reproduced the results of all-atom MD at high loading rate. GōMartini 3 is a promising tool to approach the speeds of SMFS, while preserving crucial information about the interaction between residues.

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IT–10

Interfacial recognition of lipid membranes

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We introduce evolutionary molecular dynamics (Evo-MD) simulations, an approach that merges evolutionary algorithms with the Martini coarse-grained force field. This method directs the evolutionary process from random amino acid sequences toward peptides interacting with complex fluid phases such as biological lipid membranes, offering significant promises in the development of peptide-based sensors and drugs. We demonstrate how this approach can be tailored to recognize or selectively target specific attributes such as membrane curvature, lipid composition, and membrane phases (e.g., liquid ordered phases). Although the resulting optimal solutions may not perfectly align with biological norms, physics-based inverse design excels at isolating relevant physicochemical principles and thermodynamic driving forces governing optimal biopolymer interaction within complex fluidic environments. In addition, we expound upon how physics-based evolution using the Evo-MD approach can be harnessed to extract the evolutionary optimization fingerprints of protein–lipid interactions from native proteins. Finally, we outline how such an approach is uniquely able to generate strategic training data for predictive neural network models that cover the whole relevant physicochemical domain.

Internal Normal Mode Analysis applied to flexibility, dynamics and conformational changes of biomolecules

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Normal mode analysis provides information on the equilibrium modes accessible to a system, within a harmonic approximation. It has been used for several decades in studying classical physical phenomena and the flexibility of proteins. In the past decade it has also become a tool for exploring functional motions; in particular, low frequency motions have been demonstrated to play an important role in biological processes [1]. Normal Mode Analysis can be performed with two different strategies depending on the choice of the independent variables: either considering a Cartesian coordinates space (CCS) or an internal coordinate space (ICS). The latter is more advantageous since it leads to an important reduction in the number of variables (by freezing higher-frequency bond and angle deformations) and the harmonicity of conformational energy hypersurface can be assumed over a wider range than Cartesian normal mode analysis [2,3,4]. In the case of N bodies, interbond distances and angles must be considered. Despite the advantages coming from the use of ICS, a transformation to CCS is often useful to gain insight into the overall structural changes occurring in the system. This transformation must be made so that the ICS dynamics reflect only internal motions of the molecules and no external (overall translational or rotational motions) are introduced [4]. We applied iNMA to study both proteins and RNA molecules. Regarding the former, we applied iNMA to a systematic investigation of the changes in proteins flexibility upon binding [5,6] using different coarse-grain representations [6,7], as well as to study specific systems [8]. Moreover, we analysed the capability of iNMA to predict protein motion, its intrinsic flexibility, and atomic displacements, using protein models instead of native structures, and the possibility to use it for model refinement [9]. Our studies highlighted that iNMA is a fast tool to successfully predict large conformational changes of proteins and their change of flexibility upon binding, and it represents a more suitable tool for the improvement of structural models, and for integrating them with experimental data or in other computational techniques, such as protein docking or more refined molecular dynamics simulations. As for proteins, predicting local or global changes in RNA conformations is still a challenging task. In this context, we investigated the capability of internal normal modes to reproduce RNA flexibility and predict observed RNA conformational changes and, notably, those induced by the formation of RNA-protein and

RNA-ligand complexes. Here, we extended our iNMA approach developed for proteins [5,6] to study RNA molecules using a simplified representation of the RNA structure and its potential energy [10]. Three data sets were also created to investigate different aspects. Moreover, we also investigated an application of iNMA to study large conformational changes of a biologically relevant system, such as the Cricket Paralysis Virus Internal Ribosome Entry Site (CrPV-IRES) [11]. Despite all the approximations, our study shows that iNMA is a suitable method to take into account RNA flexibility and describe its conformational changes opening the route to its applicability in any integrative approach where these properties are crucial [12].

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IT–12

Martini 3 building blocks for lipid nanoparticle design

Lisbeth Ravnkilde Kjølbye

Mechanisms of self-assembling of non-conventional surfactants by multiscale modelling and data-driven approaches.

Michele Cascella
University of Oslo

The dynamics regulating self-organisation of surface-active compounds is at the basis of the living matter; for example, it is involved into the definition of cellular boundaries, cell compartmentalisation and molecular trafficking. Surfactants are also broadly used in soft matter technology, from responsive materials, to nanodelivery. The problem associated with their characterisation at molecular level lies in the non-reducible size of the systems of interest, spanning several orders of magnitude from the nm to the m, and in their relatively long relaxation times, which can often pass the millisecond. Here, I will give an overview of recent advances in modelling of the self-assembling dynamics of surfactants, using a hierarchy of approaches at different resolution. I will discuss how external factors like ionic-strength [1], or photoactivation [2] can have a major role in controlling aggregation. I will also show how combining soft density-functional based models [3] to enhanced sampling metainference approaches [4] can be used to describe the aggregation of non-conventional surfactants that do not respect the common core-shell packing, and propose data-driven approaches for systematic calibration of such models.

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Membranes' effects on sodium channels: Nav1.7 and pain transmission

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Cholesterol is a major component of plasma membranes and unsurprisingly plays a significant role in actively regulating the functioning of several membrane proteins in humans. Notably, recent studies have shown that cholesterol depletion can also impact transmission of potentially painful signals in the context of peripheral inflammation, via hyperexcitability of the voltage-gated sodium channel (Nav) subtype 1.9, but the structural mechanisms underlying this regulation remain to be elucidated. In this study, we focus on the role of cholesterol depletion on Nav1.7, which is primarily expressed in the peripheral sensory neurons and linked to various chronic inherited pain syndromes. Coarse-grained molecular dynamics simulations shed light on the dynamic changes of the geometry of Nav1.7 upon membrane cholesterol depletion: A loss of rigidity at key structural motifs linked to activation and fast inactivation is observed, as well as changes in the geometry of drug-binding regions in the channel. Loss of rigidity in cholesterol depleted conditions should allow the channel to transition between different gating states more easily. In-vitro whole-cell patch clamp experiments on HEK293t cells expressing

Nav1.7 validated these predictions made in silico at the functional level. Hyperpolarizing shifts in the voltage-dependence of activation and fast-inactivation were observed along with an acceleration of the time to peak and onset kinetics of fast inactivation. These results underline the critical role of membrane composition, and of cholesterol in particular, in influencing Nav1.7 gating characteristics. Furthermore, our results hint to a key role of the membrane environment in affecting drug effects and in pathophysiological dysregulation, sharpening our approaches for analgesics design.

IT–15

Modeling biomolecular condensates at multiple resolutions

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Membraneless organelles are dynamical biomolecular assemblies formed via phase separation of proteins and nucleic acids. These cellular condensates are currently thought to play a major role in organizing the cellular environment and characterizing their structural and functional properties has paramount importance to improve our understanding of cell functioning. To this aim, adequate theoretical and computational approaches are needed to complement in vitro and in vivo experiments. To this respect, atomistic simulations can probe intermolecular interactions and structural ensembles in model protein and protein/RNA assemblies but coarse-grained descriptions are needed to model the condensation process of large-sized biomolecules. I will present some recent applications of coarse-grained models at various resolutions to investigate the thermodynamic determinants of the condensate assembly and for accessing their structural and dynamical details, which are elusive to most experimental techniques.

Multi-scaling and coarse graining: a bridge between materials and bio-systems

Valentina Tozzini

Multi-scale modeling is a pervasive approach, recognized necessary in all areas of the condensed and soft matter, therefore involving physis chemistry and biology. In multi-scaling, different resolution representations of the same system must talk each other with the aim of reach a compromise between accuracy and computation cost, improve transferability and predictability of the calculation, and provide an in silico picture as realistic as possible of the system under investigation1.

In this talk I will show some diverse frontiers applications, showing that multi-scaling can also act as a "bridge" between fields not commonly cross-connected. In particular, I will report on bio-graphene for water depuration derived by amyloid aggregates[2], on the multi-scale approach to the optimization of frontiers radio-therapies delivered with pulsed high dose-rate irradiation[3,4], on the development of a reduced graphene-oxide based system for green hydrogen production-storage-use[5,6], and on the design of a detector for the elusive cosmologic "relic" neutrinos from big bang[7,8][]. These apparently very distant applications share not only the use of multi-scale representations, but also the need of different simulation methodologies, encompassing advanced sampling techniques in molecular dynamics and Monte Carlo simulations, as far as advanced Force Fields optimization/parameterization, also relying on machine learning.

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Multiscale modeling of RNA inside viruses: bridging levels of resolution using minimal representations

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Modeling complete viral structures at atomistic resolution is vital for studying their stability and dynamics and can greatly help understand their folding pathway. Nevertheless, such a task involves both conceptual and technical challenges. While theoretical approaches are limited to qualitative descriptions, experimental structures provide only partial information about the arrangement of the nucleic acids in the capsid interior.

Coarse-grained models of DNA and RNA can help circumvent many of these limitations. The combination of nucleotide-level and helix-based representations has already been applied to the modeling and prediction of RNA structures of several hundreds of nucleotides [1], introducing a quick way to change the resolution of the structures. However, packaged viral RNA requires a more delicate treatment, given that additional experimental restraints must be fulfilled.

In this talk, we will address how to efficiently assemble fragments at the coarse-grained level and quickly introduce atomistic details while paying particular attention to sugar puckers and nucleobase geometries using the SPlit and conQueR (SPQR) [2] package in a confined space. In addition, we will show how to detect and remove topological entanglements that arise from the fragment assembly and are a common problem when dealing with large structures, using a standardized nomenclature [3]. Finally, we will describe how a polymer-lattice model can be used and parameterized for exploring the possible conformations consistent with experimental structures of the whole genome and some fragments inside the virus, with examples on the Satellite Tobacco Mosaic Virus, a well-known virus system ideal for testing purposes.

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Navigating the Landscape of Coarse-Grained Protein Models

Dominik Gront

Since its introduction in the early 1970s, coarse-grained modeling has been widely employed to investigate the structure and dynamics of biomacromolecules. Traditionally, these methods have been applied to explore systems and timescales that are beyond the reach of all-atom approaches. Over the decades, numerous coarse-graining approaches have been proposed. In my presentation, I will discuss several key aspects that are crucial when devising a coarse-grained model of proteins. I will highlight the choices that must be made and their associated trade-offs. These concepts will be illustrated through several algorithms developed within our research group, including SICHO, CABS, SURPASS, and SURPASS-alpha.

Ongoing Advances in the Theory and Application of Coarse-graining

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Advances in theoretical and computational methodology will be presented that are designed to simulate complex (biomolecular and other soft matter) systems across multiple length and time scales. This bottom-up approach provides a systematic connection between all-atom (AA) molecular dynamics, coarse-grained (CG) modeling, and mesoscopic phenomena. At the heart of these concepts are methods for deriving CG models from molecular structures and their underlying atomic-scale interactions. An important component of our work in the past few years has been the concept of the "ultra-coarse-grained" (UCG) model and its associated computational implementation. In the UCG approach, the CG sites or "beads" can have internal states, much like quantum mechanical states, so the UCG model involves a conceptual abstraction beyond simply Newtonian or Langevin dynamics for the CG beads. These internal states help to self-consistently quantify a more complicated set of possible interactions within and between the CG sites, while still maintaining a high degree of coarse-graining in the modeling. The presence of the CG site internal states also greatly expands the possible range of systems amenable to accurate CG modeling, including quite heterogeneous systems such as aggregation of hydrophobes in solution, liquid-vapor and liquid-solid interfaces, and complex self-assembly processes such as occur for large multi-protein complexes. The development of bottom-up CG models from the underlying atomistic interactions also addresses special challenges in terms of the treatment of solvation, multi-body correlations, representability, transferability, and the missing entropy in CG models. Recent breakthroughs in addressing these issues – in particular by employing developments in machine learning – will be a focus of my talk. As time allows, one "pay-off" application from our multi-year effort will focus on processes in HIV-1 virus replication, and especially on the assembly of the HIV-1 virus capsid from over one thousand proteins – a phenomenon involving a billion atoms or more over long timescales that cannot be approached through AA MD simulation.

On the simplification of dynamics in molecular systems

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Simplification of dynamic systems has numerous biological applications, from protein domain detection [1] to automatic coarse-graining in molecular simulations [2, 3]. Various solutions have been proposed for this problem, such as using graph theory [4-5], examining the covariance patterns in elastic network models [6], employing machine-learning-based approaches [7], or developing specific techniques based on knowledge of multiple protein conformations [8]. I will present our approach based on nonlinear normal-mode analysis with several biological applications including fitting atomistic models into SAXS and AFM data [9]. I will also present the results of the Elixir implementation study, where we examined existing strategies for dealing with multi-conformer proteins from the same family and created new techniques for analyzing the collected structural ensembles [10].

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IT–21

Perspective on simulating whole cells with Martini

Siewert-Jan Marrink

Recent development of SPICA force field and its application studies.

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The SPICA force field is a top-down coarse-grained model, where the interaction parameters are optimized for multiple target properties (such as interfacial tension, density, transfer-free energies, and distribution functions obtained from all-atom molecular simulations). The previous protein model showed limited accuracy when applied to intrinsically disordered proteins (IDPs) and peripheral proteins, because the dimensions of the IDPs in an aqueous solution were too compact, and protein binding on the lipid membrane surface was overstabilized. We introduce protein secondary structure-dependent nonbonded interaction parameters to the backbone segments and reoptimize almost all nonbonded parameters for amino acids.[1] The improved FF proposed here successfully reproduces the radii of gyration of various IDPs, the binding sensitivity of several peripheral membrane proteins, and the dimerization-free energies of several transmembrane helices. The new model also shows improved agreement with experiments on the free energy of peptide association in water. In addition, an extensive library of nonbonded interactions between proteins and lipids, including various glycerophospholipids, sphingolipids, and cholesterol, allows the study of specific interactions between lipids and peripheral and transmembrane proteins. If time permits, I would like to discuss the simulations using an alternative force field, pSPICA, based on the polar water model,[2] which is particularly needed to reproduce the structure and stability of pores and channels through lipid membranes.

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Residue-based coarse-graining of peptides and proteins: From traditional simulations to direct conformational sampling via machine learning.

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Recent progress with the development and application of CG models of proteins and RNA is presented. One area of focus is the modeling of intrinsically disordered peptides (IDP)s via COCOMO which can predict the concentration-dependent formation of biomolecular condensates and allow systematic studies of the sequence determinants of condensate formation. Extensive conformational sampling of IDPs via COCOMO simulations was also the starting point for developing generative machine learning models that can rapidly generate conformational ensembles according to a given CG model without the need for simulations. Finally, we will also briefly introduce new tools based on machine-learning for rapidly converting CG models to accurate atomistic models. We will discuss implications for implicit multi-scale sampling and coarse-graining strategies and demonstrate the rapid refinement of structural models against cryoEM density maps as a practical example.

Using Coarse-Grained simulations to understand self-assembly in biomolecular processes

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One of the most fascinating facts in biology is that all biological processes occur through self-assembly phenomena, a fundamental biological design process by which an organized structure is built from a disordered collection of smaller moieties. Yet, self-assembly processes are very challenging to monitor at an atomistic level due to the lack of resolution in current experimental setups. Moreover, such processes happen at a minimum of several micrometers and microseconds, which is beyond the reach of standard atomistic MD simulations. In this talk, I will discuss the application of the Martini force field to study the self-assembly of model biological membranes, nanoparticle-membrane systems, and proteins. Self-assembled bilayers quantitatively reproduce experimental observables, such as lateral diffusion of lipids, electron density, are per lipid and lipid order parameters.[1,2] When several anionic NPs are embedded in a model membrane, they self-assemble to form linear clusters, or chains, which were later confirmed experimentally through Cryo-TEM.[3,4] We analyze the driving forces for this self-assembly and offer an explanation based on the recently discovered orderphobic effect. We will further explore the free energy landscape of membrane protein dimerization using parallel metadynamics simulations and coarse-grained force fields and reproduce the structure and energetics of the dimerization process of membrane proteins and proteins in an aqueous solution in reasonable accuracy and throughput. We propose that the use of enhanced sampling simulations with a refined coarse-grained force field and appropriately defined collective variables is a robust approach for studying the protein dimerization process, although one should be cautious of the energy minima ranking.[5] We further apply this protocol to study protein dimers of unknown structure.

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UNICORN – UNIfied COarse gRaiNed Model

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The UNIted COarse gRaiNed (UNICORN) model is a coarse-grain model for the most important biomolecules. It originates from the UNited RESidue (UNRES) force field, which is a well-established force field for protein simulation and has been constantly developed for over 30 years. In 2013, the UNRES model was adapted to nucleic acids, resulting in the creation of the NARES-2P force field. Recently, the SUGRES-1P force field for sugars was developed, and the MARTINI membrane was adapted. However, the interactions between cellular components were missing. In 2018, interactions between nucleic acids and proteins were introduced. This started a new force field - the UNIted COarse gRaiNed (UNICORN) force field for all the most important cellular components: proteins, nucleic acids, sugars, lipids, and ions (Figure 1). In the current version, protein-lipid, protein-sugars, protein-nucleic acids, and protein-ions are implemented. In the presentation, the UNICORN model will be discussed, and the current state of UNICORN development (Fig. 1) will be shown with a description of current biological applications and limits. This work was supported by NCN OPUS 2017/27/B/ST4/00926.

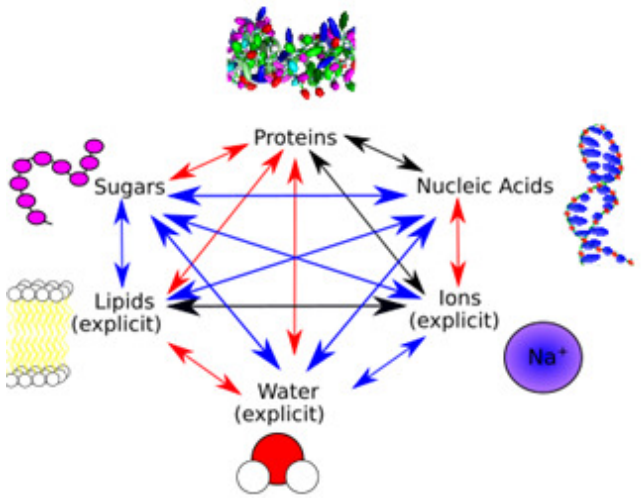

Figure 1. The UNICORN force field components. The red arrows indicate interactions that are currently being implemented. The black arrows indicate interactions that are already implemented. The blue arrows indicate interactions that are still to be implemented.

Company Talk Abstracts

CT–1

Modeling coarse-grained systems with the SAMSON platform

Stephane Redon
OneAngstrom

This talk will demonstrate the latest developments in the SAMSON molecular design platform, focusing on advancements in coarse-grained modeling. In particular, we'll discuss how to use SAMSON for importing, visualizing, editing and simulating coarse-grained models with the MARTINI force-field.

Bottom-up coarse-graining: Theory and selected applications

Reinier Akkermans
Dassault Systèmes

Materials Studio is a software package for simulating and modeling materials, from the quantum scale to the meso- and microscales. Molecules can be sketched in the visualizer, and coarse-grained to a bead representation automatically. Such "mesomolecules" can be packed in templates for bilayers, micelles, liposomes etc., ready for simulation using coarse-grained, dissipative or granular dynamics. We will highlight example workflows using the Martini3 forcefield, simulated with the Mesocite module.

Young Researcher Talk Abstracts

Strings to Systems

Fabian Grunewald
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The Simplified molecular-input line-entry system (SMILES) has become an integral part of the theoretical molecular sciences since its inception in the 1980s. A SMILES string allows researchers to represent the connectivity and atomic composition of molecules in a single string format. In a sense, the SMILES string encodes all information of the molecular graph but 3D coordinates. The shortness of the notation and the fact that it is human-readable contributed to the success of SMILES. However, for large polymeric molecules, this notation poses serious drawbacks. The size of polymer molecules often results in hardly (human) readable strings and no mechanism for dealing with the statistical nature or enantiomers is available. To overcome these problems, Lin, Olsen, and coworkers proposed the so-called BigSMILES notation and the later extension of Generative-BigSMILES. Additional descriptors representing for example statistical bonding and a fragment replacement syntax, allow a more condensed notation and deal with polymer-specific properties. Molecular simulations of polymers on the other hand are often done using coarse-grained (CG) models, which cannot be captured using such notations. To this end, we developed CGBigSMILES. This notation builds on the idea of BigSMILES and extends it to represent arbitrarily complex molecules at any level of CG resolution, the mapping from an all-atom molecule, and ultimately also the all-atom molecule itself. By implementing a CGBigSMILES API into the polyply Python package, the string can be read and converted into more universal data formats such as NetworkX graphs. Additionally, the force-field independent coordinate generation scheme can be leveraged to produce 3D coordinates for entire polymer systems.

YT–2

Bridging Scales in Biomolecular Research: From All-Atom to Coarse-Grained Simulations of Glycosaminoglycan Interactions

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In this study, we present a comprehensive comparison of all-atom (AA) molecular dynamics (MD) simulations and coarse-grained (CG) simulations using the SUGRES-1P force field [1], physics-based model of polysaccharide chains, to analyze the interactions between the cysteine cathepsins family and heparin - a key glycosaminoglycan (GAG). Cathepsins are a family of protease enzymes critical for protein degradation in all living organisms. Their enzymatic activity may be regulated by GAGs – linear periodic anionic polysaccharides, essential for numerous biological processes, including cell proliferation, adhesion and anticoagulation [2]. By analyzing these interactions theoretically, our study leverages the high-resolution insights afforded by AA simulations [3] alongside the computational efficiency of CG approaches. A significant aspect of our work is the ongoing integration of CG simulation results into the web-based database dedicated to GAG interactions with the entire family of cysteine cathepsins using in silico methods. This integration not only enriches the database with valuable data on cathepsin-heparin interactions but also establishes a comparative framework for computational approaches in biomolecular research that could be useful for rational development of novel strategies in GAG-driven drug design.

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YT–3

Design of antimicrobial peptides self-assembled into virus-like capsids

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Over the recent past decades, the constant threat of antimicrobial resistance has encouraged the development of new drugs and strategies to combat it. However, the discovery of novel approaches for targeting many bacterial strains remains challenging. In this context, the capability of antimicrobial peptides (AMPs) to disrupt bacterial activity has been extensively explored as a potential weapon against drug-resistant bacteria. Our work proposes the design of antimicrobial peptides self-assembled into virus-like capsids for delivering drugs and antimicrobial products by using state of the art rational protein design combined with multi-scale molecular dynamics simulations.

The virus's ability to infect cells has been used as inspiration to design sophisticate delivery systems. Matssura et al.[1,2] have explored the potential of short beta-annulus peptides from the genus Sobemoviruses to self-assemble into regular virus-like capsid structures, and to use these to encapsulate anionic dyes, DNA and bifunctional proteins. Despite the mechanism of assembling and capsid structure details remains unknown, there is robust evidence that three copies of beta-annulus peptides interact with each other to form a trigonal beta-annulus structure that is at the basis of the generated capsule nano-capsule. Recently, the versatility of such peptides to form virus-like nano-capsules for antimicrobial delivering systems was explored by us in two publications.[3,4] By the use of in-silico modelling and coarse-grained molecular dynamics simulations, we reveal the ability of a modified beta-annulus peptide from the Tomato Bushy Stunt virus carrying an antimicrobial sequence to form a stable nano-capsule and to perturb a model bacterial membrane.

In our current work, sophisticate learning-based protein design methods were applied to design novel trigonal beta-annulus structures and sequences, using the topology of the beta-annulus from the Sebasnia virus as a seed of our design strategy. With high prediction accuracy, these designed peptides can form the framework needed to nano-capsule assembling. Our hypotheses have been explored by extensive full-atom and coarse-grained molecular dynamics simulations. We highlight challenges involving current coarse grained force fields in exploring these complex self-assembled nanoparticles.

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Thermo-responsive polypeptides: insights from polymer physics

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Inspired by the aggregate formation in nature, the design of new materials with tailor-made properties received huge attention due to the broad range of their applications including the fabrication of responsive bio-interfaces, controlled drug delivery, and release systems, etc. The use of intrinsically disordered protein-based polymers with high control over the protein sequence and length allows for finely tuning the corresponding phase behavior of the system. One example of such bio-polymeric materials is elastin-like polypeptides (ELPs) - artificially derived bio-polymers that mimic the hydrophobic repeat unit in the protein elastin. They typically exhibit a lower critical solution temperature (LCST) phase behavior in an aqueous environment characterized by an expanded-to-collapsed conformational change of a polypeptide chain. Here, I will first present the hydrophobic collapse and assembly of a short ELP: Gly-Val-Gly-(Val-Pro-Gly-Val-Gly)3 employing Molecular Dynamics simulations in conjunction with advanced sampling techniques with an atomistic resolution. In particular, I will discuss how the structural and dynamical properties of these ELPs vary as a function of the concentration in the vicinity of the transition, and which residues are essential for contact formation in multi-chain systems. Next, I will show how the conformational properties and free energy landscape of an ELP with the sequence (Val-Pro-Gly-Val-Gly)n changes as a function of the chain length n in the temperature range relevant to the ELP's application. Specifically, I will demonstrate how the number of intra-peptide hydrogen bonds, their spacing along the chain, and their lifetime define the conformational faith of ELPs.

Poster Abstracts

P–1

A Temperature-Dependent Length Scale for Local Density Coarse-Grained Potentials

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Most coarse-grained (CG) models rely on pair potentials to accurately describe the structure of homogeneous systems. However, they often lack transferability across different thermodynamic conditions and fail to adequately describe thermodynamics. Recent methodologies involve supplementing pair potentials with one-body local-density (LD) potentials, leading to notable improvements in modeling thermodynamic properties such as pressure and compressibility. Nonetheless, the accuracy of these models hinges on the precise definition of LD, which remains unknown a priori. Additionally, there is little understanding of how LD models vary across different thermodynamic conditions. In this study, we systematically investigate CG LD models of molecular liquids utilizing both pair and local-density potentials across a wide range of liquid-phase thermodynamic state points. Our findings reveal a temperature-dependent length scale in these models, facilitating their transferability. Specifically, adopting a temperature-dependent LD length scale renders the LD potential seemingly independent of temperature, whereas the pair potential exhibits linear variation across the temperature range. This approach offers a straightforward method for predicting pair and LD potentials capable of accurately modeling new thermodynamic conditions without necessitating additional atomistic simulations. Remarkably, our results indicate that at specific thermodynamic conditions, the predicted potentials outperform potentials optimized for those conditions.

P–2

A millisecond coarse-grained simulation approach to decipher allosteric cannabinoid binding at the glycine receptor α1

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Glycine receptors (GlyR) are regulated by small-molecule binding at several allosteric sites. Cannabinoids like tetrahydrocannabinol (THC) and N-arachidonyl-ethanol-amide (AEA) potentiate GlyR but their mechanism of action is not fully established. By combining millisecond coarse-grained MD simulations powered by Martini 3 with backmapping to all-atom representations we have characterized the cannabinoid-binding site(s) at the zebrafish GlyR-α1 active state with atomic resolution. Based on hundreds of thousand ligand-binding events, we find that cannabinoids bind to the transmebrane domain of the receptor at both intrasubunit and intersubunit sites. For THC, the intrasubunit binding mode predicted in simulation is in excellent agreement with recent cryo-EM structures, while its intersubunit binding recapitulates in full previous mutagenesis experiments. Intriguingly, AEA is predicted to bind at the same intersubunit site despite the strikingly different chemistry. Statistical analyses of the ligand-receptor interactions highlight potentially relevant residues for GlyR potentiation offering experimentally testable predictions. The predictions for AEA are validated by electrophysiology recordings of rationally designed mutants. The results highlight the existence of multiple cannabinoid-binding sites for the allosteric regulation of GlyR and establish an effective simulation protocol for the identification and structural characterization of allosteric binding sites.

P–3

Assessing The Effects Of Coarse-Grained Models for Gold On Aggregation of Nanoparticles In Lipid Bilayers

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Gold nanoparticles (GNPs) are ubiquitous photosensitizers with a broad range of applications spanning from microscopy to targeted drug delivery. In several applications, GNPs interact with the periphery of the lipid bilayer or embed between the leaflets, causing deformations to the membrane. Many interactions between lipids and nanoparticles occur over long timescales; therefore, coarse-grained (CG) molecular dynamics simulations are necessary to study GNP-Lipid systems further. Several conflicting CG models for gold have been proposed, differing in chemical nature and resolution. Many studies rely on a hydrophobic bead for the gold core, while others use polar beads or soft spheres. It is frequently presumed that aggregation behavior is dominated by the ligands that functionalize the GNP, and that systematic parameterization of the gold core itself is unnecessary. Furthermore, GNP models that have been validated in the aqueous phase are rarely retested in a membrane. Here, we compare the aggregation behavior of nanoparticles with gold cores composed of three different types of beads: polar beads, hydrophobic beads, or soft sphere beads. We use aggregation as a metric to compare the models to each other and experimental data. We find a pronounced dependence on the choice of model beads, particularly for gold nanoparticles with shorter ligands, and we observe large-scale aggregation in nanoparticles composed of polar beads that correspond most closely with experimental results. These results suggest that interactions of the GNP cores help drive gold nanoparticle interactions, particularly for shorter ligand lengths, and that a polar core model may be more suitable than a hydrophobic model for studying GNPs in hydrophobic environments.

P–4

Assessing the Performance of MARTINI Force Fields for Glycolytic Enzyme Self-assembly

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Despite the wealth of knowledge concerning the regulation and biochemistry of glycolytic enzymes, our understanding of their spatial arrangement within the cell is constrained. Previous electron microscopy experiments revealed that human phosphofructokinase-1, a highly regulated enzyme involved in glycolysis, can assemble into filaments.[1] In particular, this was found to be the case for the liver isoform (PFKL) whereas the platelet isoform (PFKP) did not form filaments.[1] Here, we evaluated the efficacy of Martini force fields in modeling the assembly of PFKL filaments, with PFKP as the comparative reference.

Our results indicate that the solution protein complexes lack stability in the current Martini 3 (v3.0.0), while Martini 2 (v2.2) and the Martini polarizable water model (v2.3P) overestimate the stability of the protein complexes. Using Martini 2 and the Martini polarizable water models, both PFKL and PFKP formed stable filaments. Although Martini 3 was unable to predict filament formation for PFKL, it appeared to estimate the interaction sites more accurately than Martini 2 and Martini polarizable water models. In our ongoing pursuits, we intend to enhance the present model of glycolytic enzyme assembly by fine-tuning protein-protein interactions in the Martini 3 coarse-grained force field.

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P–5

Bridging Scales in Biomolecular Research: From All-Atom to Coarse-Grained Simulations of Glycosaminoglycan Interactions

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This paper will be presented as a Young Researcher Talk only, see that section for the abstract.

P–6

CGCompiler: Automated Coarse-Grained Molecule Parametrization via Noise-Resistant Mixed-Variable Optimization

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ENS Lyon

Coarse-grained force fields (CG FFs) such as the Martini model entail a predefined, fixed set of Lennard-Jones parameters (building blocks) to model virtually all possible nonbonded interactions between chemically relevant molecules. Owing to its universality and transferability, the building-block coarse-grained approach has gained tremendous popularity over the past decade. The parametrization of molecules can be highly complex and often involves the selection and fine-tuning of a large number of parameters (e.g., bead types and bond lengths) to optimally match multiple relevant targets simultaneously. The parametrization of a molecule within the building-block CG approach is a mixed-variable optimization problem: the nonbonded interactions are discrete variables, whereas the bonded interactions are continuous variables. Here, we pioneer the utility of mixed-variable particle swarm optimization in automatically parametrizing molecules within the Martini 3 coarse-grained force field by matching both structural (e.g., RDFs) as well as thermodynamic data (phase-transition temperatures). For the sake of demonstration, we parametrize the linker of the lipid sphingomyelin. The important advantage of our approach is that both bonded and nonbonded interactions are simultaneously optimized while conserving the search efficiency of vector guided particle swarm optimization (PSO) methods over other metaheuristic search methods such as genetic algorithms. In addition, we explore noise-mitigation strategies in matching the phase-transition temperatures of lipid membranes, where nucleation and concomitant hysteresis introduce a dominant noise term within the objective function. We propose that noise-resistant mixed-variable PSO methods can both improve and automate parametrization of molecules within building-block CG FFs, such as Martini.

P–7

Coarse Grained Strategies to Study Angiotensin-Converting Enzyme 2 (ACE2) and its Peptide Inhibitor DX600

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Most of the methods employed in drug design have been originally introduced and optimized for the case of a small molecule interacting with a protein. As pharmaceutical research is gradually shifting its interest towards the use of short peptides instead of small molecules, the need to modify old methods or devise new ones is becoming more urgent. In this talk we show how a multiscale approach combining atomistic and coarse grained simulations is able to clarify the molecular details of the interaction between ACE2, the membrane protein acting as a receptor for SARS-CoV-2 spike, and its peptide inhibitor DX600. Three different methodological approaches to coarse-graining will be illustrated: the statistical-based one used for ACE2, the intrinsically disordered protein database-based for the linker, and the Boltzmann inversion-based one for the DX600 peptide.

Coarse-Grained Models for the interaction of Bio-Functionalized Metal Nanoparticles with Proteins

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Nanoparticles (NPs) have gained attention in theranostics for their potential functionalization with various chemical groups, enabling precise surface modifications for selective interactions with biomolecules. For example, highly charged gold NPs functionalized with cationic arginine-based ligands can form a stable complex with the highly negatively charged GFP protein, acting as a biosensor [1]. Conversely, highly hydrophobic gold NPs functionalized with the amino acid phenylalanine have been proposed as antiaggregants for beta-microglobulin [2]. However, the effectiveness of these NPs depends on size, charge, hydrophobicity and environmental conditions (ionic strength, temperature), requiring optimisation. For this task, coarse grained models are essential to study aggregation properties of these systems, overcoming the challenges of experimental complexity and high computational costs associated with atomistic simulations.

Minimalist models for proteins, in which each amino acid is represented with a single bead and parametrised using a combined bottom-up/top-down strategy, have already been constructed [3]. However, there is a scarcity of coarse-grained models for NPs: some models represent NP with a single sphere, lacking accuracy in reproducing proteins interactions [4], other have a resolution that is too high[5], making them inefficient and incompatible with minimalist protein models. In this poster, I will focus on constructing coarse-grained models for phenyl-functionalized NPs and cationic arginine-functionalized ones, utilising a multiscale approach [6]: relevant information, such as electrostatic potential and distribution functions, are extracted from atomistic simulations and used to parameterize the coarse grained model. This study pays attention to the compatibility in level of resolution and parametrisation strategy with existing models of GFP and beta-2-m proteins. The obtained models have been tested in different environmental conditions and are transferable to other NPs with different charge and hydrophobicity. This marks a preliminary step toward using them for studying the aggregation with proteins, aiming to identify conditions for optimal theranostic efficacy.

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P–9

Coarse-Grained System Builder (CGSB): A tool for accurate construction of coarse-grained simulation systems

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The creation of a system is one of the most critical parts of conducting molecular dynamics simulations, as the system composition determines the simulation outcomes. Complex asymmetric membranes are particularly problematic to construct, as they require preservation of not only the lipid ratios inside the leaflets but also between them while operating only with a whole number of lipids. In smaller membranes, this trade-off can lead to severe ratio drifts from the requested values. Here we present a new Python tool, CGSB, that addresses these issues by ensuring accurate interleaflet lipid ratios, as well as optimization of the ratios within a given leaflet. On top of that, the tool handles multiple proteins and membranes within the same system, allows for easy importation of custom lipids and small molecules, and can perform solute flooding and solvation procedures. It can easily create phase-separated membranes of complex shapes, phase-separated solvents, stacked membranes, and nanodiscs. Developer-friendly features of CGSB include multiple parameter libraries that can be mixed and matched within the same system, if necessary. CGSB can be run both from a command line and within a Python environment. The source code, documentation, and tutorials are available at https://github.com/MikkelDA/CGSB.

P–10

Coarse-grained molecular dynamics simulations of liquid-liquid phase separation of intrinsically disordered protein

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Liquid-liquid phase separation (LLPS) is a spontaneous process in which solute molecules within a solution aggregate into liquid droplets or condensates. These phenomena are particularly noteworthy in eukaryotic cells, where certain condensates, devoid of a lipid membrane and termed membraneless organelles (MLOs), play crucial biological roles. Notable examples include nucleoli, stress granules, P-bodies and so on [1,2].

Intrinsically disordered proteins (IDPs), with their highly flexible and dynamic structures and the ability to make multivalent interactions, are closely associated with LLPS and bio-condensate formation [3]. Depending on the sequence of these IPDs, their phase separation is finely regulated by environmental factors such as temperature, pH, salt concentration, or specific small molecules.

However, the intricate interplay of intramolecular and intermolecular interactions that governs these modulations still remains elusive. Tempetarure-responsive IDP low complexity sequences, exhibiting reversible changes in solubility as a function of temperature, provide a promising avenue gain insight into the physical and chemical factors that regulates their LLPS. In this communication, we present a temperature-transferable coarse-grained (CG) model, specifically optimized to efficiently reproduce both upper critical solution temperature (UCST) and lower critical solution temperature (LCST) behaviors of different IDPs [4].

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P–11

COARSE-GRAINED SIMULATIONS FOR THE STUDY OF MOLECULAR MECHANISMS OF IMMUNE DISEASES

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We aim to shed light into the distinct molecular interactions that lead to immune-related diseases. We have explored allergy, the immune response that occurs to innocuous proteins like Pru p 3, a peach protein and model in food allergy. A significant proportion of known allergens are lipid transfer proteins (LTPs) like Pru p 3, and recent compelling evidence suggests that their lipidic ligands might play a key role in triggering allergy. By means of coarse-grained (CG) molecular dynamics (MD) simulations we described the membrane binding domain of Pru p 3 where the uptake of its ligand takes place, and we revealed its preferential interaction with anionic membranes driven by electrostatic interactions [1]. In parallel, we addressed the effect of the diverse chemical structures of lipid A of lipopolysaccharides (LPS) from gram-negative bacterial membranes in the modulation of the physico-chemical properties of the membrane and permeability to antibiotics, critical mechanism for the antimicrobial resistance (AMR) [2]. We have built, by CG MD calculations, liposomes as models of outer and inner membrane vesicles of ESKAPE pathogens, the most dangerous AMR bacterial families according to the WHO, capturing the role of lipid A, cardiolipin and cholesterol on liposome morphology and physico-chemical properties. Additionally, the reported antimicrobial peptides Ceropin B1, JB95, and PTCDA1-kf, were used to unveil their implications on membrane disruption [3]. In summary, CG MD analysis have allowed us to provide key insights into immune-related diseases such as allergies and antimicrobial resistance, enhancing our understanding of immune mechanisms and opening avenues for novel therapeutic strategies.

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P–12

Comparative Exploration of nucleosome Dynamics using All-Atom and Coarse-Grain Approaches

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In the eukaryotic cell, the most important packaging unit of DNA is the nucleosome. The core portion of nucleosome i.e., nucleosome core particle (NCP) is a large complex of 145-147 base pairs of DNA and eight histone proteins [1]. The dynamics of the NCP is associated with timescales of microseconds to seconds [2,3]. Hence, the high computational cost of atomistic molecular dynamics (MD) simulation to explore the dynamics is computationally challenging. Motivated by this, here we probe the structural and dynamic properties of the NCP using state-of-the-art coarse-grained (CG) force field SIRAH [4]. We perform long-time CG MD simulations of the NCP at physiological ion concentrations. We compare various structural parameters for both DNA and histone protein obtained from CG simulation with all atom simulation. Initial results also show breathing motion (transient opening/closing of the DNA end region) within the simulated timescale for the human a-satellite palindromic (ASP) (PDB ID: 1KX5) nucleosome sequence. We further characterize breathing motion in terms of breathing distance as well as DNA translocation and rotational order parameters [5]. We also performed umbrella sampling to obtain the free energy landscape during the unwrapping of nucleosomal DNA. We further compare this with all atom results. To understand the interplay between DNA sequence and nucleosome dynamics, we also explore the NCP dynamics on another well-known sequence, Widom-601 (PDB ID: 3LZ0), using the CG approach. Our findings can help unveil DNA dynamics within large bio-macromolecular complexes like the NCP.

Conditional Normalizing Flows for Active Learning of Coarse-Grained Molecular Representations

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Efficient sampling of the Boltzmann distribution of molecular systems is a long-standing challenge. Recently, instead of generating long molecular dynamics simulations, generative machine learning methods such as normalizing flows have been used to learn the Boltzmann distribution directly, without samples. However, this approach is susceptible to mode collapse and thus often does not explore the full configurational space. In this work, we address this challenge by separating the problem into two levels, the fine-grained and coarse-grained degrees of freedom. A normalizing flow conditioned on the coarse-grained space yields a probabilistic connection between the two levels. To explore the configurational space, we employ coarse-grained simulations with active learning which allows us to update the flow and make all-atom potential energy evaluations only when necessary. Using alanine dipeptide as an example, we show that our methods obtain a speedup to molecular dynamics simulations of approximately 15.9 to 216.2 compared to the speedup of 4.5 of the current state-of-the-art machine learning approach.

P–14

Conformational exploration of HSULF-2, an Intrinsically Disordered Protein (IDP): benchmarking of coarse-grained models

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Human endosulfatase 2 (HSULF2), a newly discovered sulfatase at the beginning of 21st century[1], is implicated in numerous physiopathologica[1] processes, such as breast cancer and inflammation. However, little is known about the 3D structure of this enzyme at the atomic level. Until now, the only available 3D structure is the one predicted by AlphaFold2 (AF2). Indeed, no experimentally resolved structure has been yet uploaded in the Protein Data Bank (PDB), which can be attributed to the fact that its hydrophile domain (HD) is an intrinsically disordered region (IDR). Therefore, it remains critical but always challenging to obtain HSULF2 structure either experimentally or computationally.

We are collaborating with biochemists of our laboratory LAMBE who are characterizing HSULF2 structural features using mass spectroscopy[2–4]. Their results can be integrated into the AF2 model. In addition, HSULF2 enzymatic activities, such as substrate binding specificity and the modified activities of several mutants, are actively investigated experimentally. Interpreting these results often requires an extensive understanding of protein flexibility and dynamics. Coarse-grained models are adapted for this study, as the simplification enables phase space to be explored more rapidly. Therefore, we are exploring the conformational space of HSULF2 using several coarse-grained models: MARTINI3, SIRAH, UNRES, and CALVADOS. One important measure of global compacity is the radius of gyration R(g), which was previously experimentally determined at the LAMBE. We thus compare the R(g) from molecular dynamics simulations with this experimental value to benchmark the different CG models.

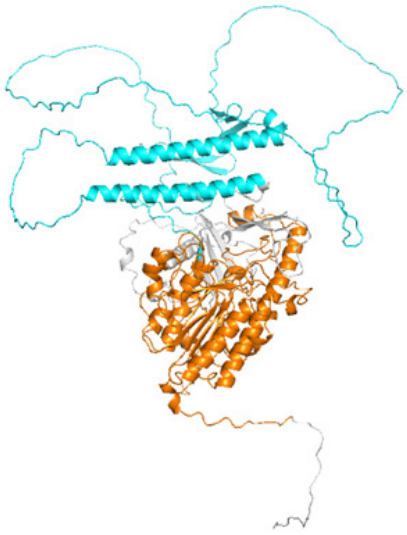

Figure 1. 3D structure of HSULF2 predicted by AlphaFold2. Hydrophile Domain is colored in cyan, where high disorder is observed.

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P–15

Design of Viral Capsid Assembly

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A virus particle consists of two primary components: nucleic acid and a protective protein coat known as a capsid. Capsids, composed of tens to thousands of protein subunits called capsid proteins, spontaneously assemble even in densely populated cellular environments. Natural capsids are stabilized by protein–protein interfaces that have evolved to be efficient self-assembling unit having multiple interfaces (multivalency). The hierarchy of strengths of interactions in these interfaces are carefully selected by nature in such way that it allows error-corrected assembly without any off-pathway aggregated states. Our research aims to unravel the mechanism governing viral capsid assembly using molecular simulations. We are developing a minimal coarse-grained model where interfaces are represented by interacting patches and non-interfacial residues are represented by volume excluding spheres. Based on the principles obtained from the efficient natural system using minimal coarse-grained simulation, we intend to modify the monomers to redesign a capsid assembly process for biomedical applications such as developing new drug carriers and vaccines.

P–16

Design of antimicrobial peptides self-assembled into virus-like capsids

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This paper will also be presented as a Young Researcher Talk, see that section for the abstract.

P–17

Design of red-shifted imaging crystallophores for protein crystallisation

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X-ray diffraction is the most widely used method to date for determining the three-dimensional structure of proteins. It is therefore necessary to obtain good quality protein crystals. We have developed lanthanide complexes called crystallophores, [1] which are a useful auxiliary for protein crystallization, a complicated and unpredictable process. This first generation of TbXo4 crystallophores made it possible to determine the structures of unknown proteins. [2] The second generation aims to facilitate crystal detection using the intrinsic luminescence propriety of f-elements. [3] We discuss the challenges of developing imaging crystallophores with different red-shifted spectroscopic properties and our first steps in modelling their interactions with proteins.

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Elucidating hierarchical interactions in phase-separated condensates with multi-scale simulations

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Phase-separated condensates, in the form of germ granules, play a role in modulating gene expression by binding with cofactors during germ cell development. By preventing the relocalization of their binding partners into the residual body, they influence the inheritance of RNA molecules via sperm into the embryo. To understand their importance and their function, we investigate both the formation of germ granules out of scaffold proteins as well as the underlying mechanism of how specific Argonaute proteins localize to condensates. Previous experiments by the Ketting lab have highlighted the importance of PEI-1 and PEI-2 for the specific recruitment of Argonaute proteins such as WAGO-3 to germ granules. We aim to complement experiments with multi-scale modeling spanning the full bandwidth of atomistic molecular dynamics to capture highly specific interactions and coarse-grained simulations of the behavior of multiple phase-separated droplets. Importantly we will account for the hierarchical interplay of interactions (among different domains of proteins, protein monomers, granules as well as their binding partners) in multiscale models and study the effect of hierarchical interactions on material properties and ultimately biological function. We present the first steps towards the identification of molecular interfaces modeling strong and specific interactions between folded domains that remain present over longer time scales, as well as dynamic but multivalent interactions in intrinsically disordered domains. The first atomistic simulations highlight flexible parts of PEI-1 and PEI-2. Large-scale atomistic and coarse-grained simulations of PEI-1 and PEI-2 folded domains potentially will shed light on to what extent specific interfaces enhance the formation of multimolecular structures.

P–19

Estimation of thermophysical properties of protein self-association with improved coarse-grained force fields

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Characterization of weak non-specific interactions and associated thermophysical properties of proteins is essential for both folded and disordered proteins to understand their complex behaviors and functions in solution. Coarse-grained molecular dynamics simulations are an effective way to study protein self-association behavior at large length and time scales. However, the effectiveness of these simulations depends on a sufficiently accurate force field that can replicate the structural attributes of disordered proteins and also has well-balanced protein-protein interactions. Explicit water coarse-grained (CG) force fields often overestimate protein-protein interactions. We use two force fields for this purpose, SPICA and Martini 3, for both of which recent developments have improved protein-protein interactions.

Experimental data informs computational protein cluster prediction in Mitochondria

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Weria Pezeshkian
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Mitochondria are widely known as the powerhouse of the cell and, thus, a vital membrane-bounded organelle. Besides its key function in energy metabolism, it is also involved in various other cell functions and pathways, like intracellular signaling, cell growth, and cell death. A double membrane shields a mitochondrion from the rest of the cell, with the inner membrane weaving through the whole organelle's body, forming compartments. The membranes, the intermembrane space, and the so-called matrix, the space surrounded by the inner membrane, contain an abundance of proteins in varying densities, which form complexes that mediate the different processes in mitochondria. However, while functions and pathways (in health and disease) are still found, corresponding complexes must be discovered.

To probe protein complex formation in Mitochondria, we employ molecular dynamics simulations, in which the potentials governing the interactions are directly informed by data obtained via a cross-link mass spectrometer, including the number of links and abundance of protein type. The simulations include representations of proteins bound to the membranes and freely moving proteins from the inter-membrane and matrix domain approximating their natural environment. Different protein complexes form through several simulations on membranes and the soluble compartments. We will find that the known complexes are recovered while other new complexes make an appearance. The new complexes might then be experimentally identified, and other functions of Mitochondria might be explained.

Extension of the SUGRES-1P Coarse-Grained Model of Polysaccharides to Heparin

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Heparin (HP), a member of the glycosaminoglycan (GAG) family, is an unbranched periodic polysaccharide composed of negativelycharged disaccharide units involved in key biological processes including anticoagulation, angiogenesis and inflammation via interactions with its protein targets in the extracellular matrix. Although all atom molecular dynamics (MD) simulations allow for efficient analysis of protein-GAG interactions [1], long chains of GAG polysaccharides participate in many biologically relevant processes at much bigger scales and longer times than the ones which all atom MD is able to effectively deal with. Among these processes is establishment of chemokine gradients, amyloidogenesis or collagen network organization. To make modeling of such processes feasible, a conceptually different approach is needed. In these terms, application of coarse-grained approaches is potentially promising to model big HP-containing molecular systems at longer timescales. We have extended the coarse-grained SUGRES-1P model of polysaccharides [2] to HP and modified the interaction energy function to account for a shift of the interaction centers and to enable a direct modification of the electrostatic energy term weight. With this modification, we were able to apply the SUGRES-1P force field in microsecond-long MD simulations of free HP oligosaccharides ranging from degree of polymerization 6 to 68. The modeled HP chains exhibited remarkable similarity to experimentally determined HP molecules [5,6] in terms of their global structural characteristics. We integrated the SUGRES-1P model into the coarse-grained UNICORN model [7], enabling microsecond-scale MD simulations of HP interactions with proteins. Analyses of several benchmarking protein-HP complexes allowed us to obtain an ensemble of structures that effectively captured the dynamic nature of the interacting protein and HP oligosaccharides. This achievement represents a significant milestone, as it is the first time a "bottom-up" physics-based approach has been used for coarse-grained modeling of HP chains, while maintaining compatibility with other biomolecule classes within the UNICORN modeling package.

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P–22

Metainference simulations to interpret small-angle scattering experiments of non-conventional surfactants

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In the study of soft-matter systems, measurements performed in solution using, e.g., small-angle scattering are very important. Information on the size, shape, and dynamics of the system, can be obtained through modeling of small-angle neutron scattering (SANS) and small-angle x-ray scattering (SAXS) experiments. However, some systems can be challenging to model, due to non-conventional packing or polydispersion. In such cases, molecular dynamics (MD) simulations can help, but often the force fields do not reproduce the correct structural ensemble, or the events happen in a time scale longer than simulation times. Metainference is a Bayesian inference method that enhances the sampling of MD simulations through bias forces that drive the models towards improved agreement with the experiment. The goal is to sample configurations that represent the correct ensemble and, on average, obtain agreement with the experiment. Recently, some of us have extended Metainference to allow using SANS data. Here, we present the first study on surfactant aggregation combining SAXS and SANS Metainference MD simulations. We study Triton X-100, a detergent that has been previously studied in the literature, and for which there is no consensus on the formed micelles' size and shape. This is due to the non-conventional structure of the micelles, which cannot be described by a simple core-shell model, and polydispersion. A polydispersion of aggregates with sizes varying from 3 to 129 molecules is necessary to reproduce the SAXS and SANS spectra simultaneously. Triton X-100 micelles show shapes dependent on their size, with the smaller being rather spherical and the larger being irregular (oblate or triaxial shape). For some sizes, the hydrophobic part shows an onion-like structure. This case study illustrates how Metainference can aid the interpretation of small-angle scattering experiments.

P–23

Modeling photoswitches in membranes and proteins at coarse-grained resolution

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Azobenzene is a prototypical photoswitchable molecule which can be isomerized from its trans- to its cis-configuration and vice versa by means of light. In recent years, the incorporation of such photoswitchable moietyies in biomolecules like lipids or protein ligands enabled the control of membrane properties and protein activity, respectively.

We used molecular dynamics simulations at coarse-grained resolution with the Martini 3 force field to study the properties of lipid membranes containing photolipids as well as a photoswitchable protein inhibitor. To this end, we developed Martini 3 models for azobenzene and diazocene, which successfully reproduce the conformational changes upon photoswitching, and incorporated them in photolipids as well as protein inhibitors.

Our coarse-grained simulations of the photolipids in model membranes provide a direct molecular view on the changed membrane properties such as thickness, lipid tail order, and area per lipid. The photoswitchable inhibitor stably binds to the protein pocket and we observe unbinding for the cis-isomer which experimentally is expected to exhibit reduced affinity. Moreover, we observe rebinding events in our unbiased trajectories.

P–24

Molecular mechanism of lipid droplet biogenesis

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Lipid droplets (LDs) are organelles that regulate energy and lipid metabolism within cells. LDs formation primarily occurs in the tubular areas of the endoplasmic reticulum (ER), where neutral lipids like triglycerides accumulate in lens-shaped blisters. Once the nascent LD grows beyond a specific threshold, it buds from the ER membrane, towards the cytosol. However, the budding mechanism has never been experimentally observed. Here, we developed a new, reliable computational methodology that simulates the initial steps in LD biogenesis, from LD nucleation to budding. Simulations revealed that LDs require a certain degree of asymmetry between the two membrane leaflets to bud, regardless of membrane morphology. Seipin, an essential protein for proper LD function, promotes an asymmetric shape of nascent LDs but is not sufficient to promote budding on its own. Instead, seipin increases the mechanical stability of the LD-tubule connection. Additionally, simulations highlighted the crucial role of the ER's oil/phospholipid synthesis ratio in preserving the mechanical stability of the network and ensuring a stable LD-tubule connection. This novel computational methodology will enable simulations of more complex membrane system transformations. This study sheds light on the early stages of LD biogenesis and provides insights into the factors that contribute to this process.

P–25

Multi-eGO: Make structure-based models great again

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Structure-based models have been instrumental in simulating protein folding and suggesting hypotheses about the mechanisms involved. Today, at least for fast folding proteins, folding in explicit solvent can be simulated using classical molecular dynamics. However, more complex folding or other processes such as self-assembly or protein aggregation are still far from being accessible on feasible timescales. Multi-eGO, a hybrid multistate structure-based model, could help to bridge the gap towards the simulation of out-of-equilibrium complex folding and concentration-dependent self-assembly processes.

P–26

Multi-state dynamics of the allosteric cycle of Hsp70

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Heat shock proteins are one of the most important biological families, involved in a wide range of molecular events. They play a crucial role in many key biological processes inside living cells, such as protein folding, degradation and assembly processes(1). In particular, we decided to focus on Hsp70 cycle activity, trying to characterize it from a mechanistic perspective. Hsp70 uses ATP binding at the nucleotide-binding domain (NBD) and its successive hydrolysis to control and promote binding/release events of clients at the substrate-binding domain (SBD)(1,2). A complete view of this complex allosteric mechanism is still lacking. Recently, some experimental studies have characterized quantitatively key movements between Hsp70 domains by means of FRET analysis on residue-pair distances(2). We decided to explore the Hsp70 dynamics through a multi-scale computational approach with all-atom simulations(3) and different coarse-graining techniques(4,5). Driven by experimental information based on FRET analysis we will finally test our models in order to better understand dynamical conformation and allosteric pathways of Hsp70.

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P–27

Multiscale modeling of ADAM10-lipids interactions during apoptosis

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Apoptosis is essential for organismal development, tissue homeostasis and elimination of pathogen-infected cells. Biochemical data has shown that the induction of apoptosis in both transformed and primary human T cells leads to rapid and selective cell surface removal of mucins by the sheddase ADAM10[1]. While the fact that negatively charged lipids need to be exposed to the cell surface for this process to occur is well established, the role of these lipids in ADAM10 sheddase activity is currently unknown. ADAM10 is a transmembrane protein whose extracellular domain has been characterized in 2017 using crystallography[2], showing a completely folded structure with a buried catalytic domain.

Recently, an open structure of the protein has been characterized using cryo-EM[3], suggesting that the opening of the protein is essential for its activity. In addition, ADAM10 is known for its ability to form dimers in the membrane[4], but the effect of dimerization is not depending on its TM domain, which raises additional questions about the interplay between the protein and the membrane components.

Here we propose a multiscale computational modeling approach, using All-Atom (AA) and Coarse-Grained (CG) molecular dynamics simulations, to resolve the mechanism of lipid-induced sheddase activation. Using extensive enhance sampling molecular dynamics simulations at the AA scale, we aimto characterize the dynamics of ADAM10 depending on the membrane composition. We will then use the results of our AA simulations to establish our CG model of ADAM10 which will be instrumental to understand the membrane mechanisms regulating the activity of the protein.

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P–28

OLIVES: A Gō-like Model for Stabilizing Protein Structure via Hydrogen Bonding Native Contacts in the Martini 3 Coarse-Grained Force Field

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Coarse-grained molecular dynamics simulations enable the modeling of increasingly complex systems at millisecond timescales. The transferable coarse-grained force field Martini 3 has shown great promise in modeling a wide range of biochemical processes, yet folded proteins in Martini 3 are not stable without the application of external bias potentials like elastic networks or Gō-like models. We herein develop an algorithm, called OLIVES, which identifies native contacts with hydrogen bond capabilities in coarse-grained proteins, and use it to implement a novel Gō-like model for Martini 3. We show that the protein structure instability originates, in part, from the lack of hydrogen bond energy in the coarse-grained force field representation. By using realistic hydrogen bond energies obtained from literature ab initio calculations, it is demonstrated that protein stability can be recovered by the reintroduction of a coarsegrained hydrogen bond network and that OLIVES removes the need for secondary structure restraints. OLIVES is validated against known protein complexes, and at the same time addresses the open question of whether there is a need for protein quaternary structure bias in Martini 3 simulations. It is shown that OLIVES can reduce the number of bias terms, hereby speeding up Martini 3 simulations of proteins by up to ≈ 30 % on GPU architecture compared to the established GōMARTINI model.

P–29

Paving the way for modelling coarse-grained carbohydrates with a systematic approach

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Coarse grain modelling of macromolecules is an active research field that aims to answer questions ranging from physics to biology. Martini is one of the most popular coarse-grained(CG) force fields that has parameters for the main biological molecules (lipids, solvent, proteins, nucleic acids, carbohydrates, and some small molecules). Notably, there has been a substantial change in the latest Martini release -Martini 3- where the mapping, bead types and interaction levels were redefined[1]. In this work, our focus is on expanding the existing Martini 3 monosaccharide parameters[2] to an extensive set of disaccharides. The parametrisation was based on the existing Martini 3 bead types and atomistic simulations of combinations of disaccharides to infer the coarse-grained bonded parameters. The mapping choice followed the generic Martini 3 rules of bead assignment, keeping an overall 4:1 resolution (4 heavy atoms for 1 CG bead), but also made use of smaller beads for the ring beads and some substituents. Secondly, we also parametrised E.coli lipopolysaccharide (LPS) for Martini 3 force field to study microbiologically relevant systems. The first step involved modelling Lipid A, followed by Re-LPS (which consists of Lipid A plus two molecules of KDO). With this work, we aim to give a framework to model coarse-grained carbohydrates and carbohydrate-linked molecules such as post-translational modifications and glycolipids. Having a generic set of disaccharides as well as approaches to build higher order molecules will be truly beneficial for the modelling community given the high complexity and structural heterogeneity of glycomolecules.

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P–30

Protein-Protein interactions in the Purinosome Metabolon

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Purine synthesis consists of two pathways, the salvage pathway, which operates under normal physiological conditions, and de novo synthesis. The latter comes into play when purine levels are depleted, triggering a more energetically intensive pathway in which the purinosome is assembled1.

The purinosome is a case of a metabolon, where metabolic enzymes are spatially and temporally organized into multi-enzyme complexes. This has plenty of advantages, but a remarkable one is that the substrates can be transferred directly from one active site to another, a phenomenon known as "channeling"2.

In de novo synthesis, ten chemical steps are involved in converting phosphoribosyl pyrophosphate (PRPP) into inosine monophosphate (IMP), with the participation of six enzymes. These enzymes form a complex and reversibly compartmentalize within cells during specific stages of the cell cycle1.

By employing molecular dynamics simulations at a coarse-grained level, we explored two different scenarios for the purinosome. In fact, in the absence of an experimental quinary organisation of the six enzymes, we were forced to generate the spatial organization of the complex. We constructed two scenario. In each scenario, we conducted geometrical and spatial analyses to assess their respective advantages and disadvantages. While many studies have attempted to determine the size of one single purinosome, consensus suggests it is unlikely to exceed 300 nm in diameter3. Our studies, however, reveal significant deviations from these results.

Furthermore, we conducted studies to investigate the behavior of the first ligand in the reaction, phosphoribosylamine (PRA), within PRPP. Consequently, an analysis of how it behaves upon encountering its binding site in the second protein of the pathway provides clear evidence of the importance of the channeling mechanism.

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P–31

Reviving Ions: A coarse-grained SPICA-FF makeover for sodium and chloride ions

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Aqueous ionic solutions, where water serves as the solvent and ions act as solutes, are pivotal in various scientific domains due to their natural prevalence and vital roles in biological and chemical processes. Molecular dynamics has emerged as an effective methodology for studying the dynamic behavior of these systems. While all-atomistic models have made significant strides in accurately representing and simulating these ions, the challenge persists in achieving precise models for coarse-grained simulations. To address this challenge, our study introduces two optimized models for sodium and chloride ions within the non-polarizable surface property fitting coarse grained force field (SPICA-FF) framework. The two models represent solvated ions, like the original force field (FF) model, and unsolvated or bare ions. The non-bonded Lennard-Jones interactions were re-parameterized to faithfully reproduce bulk properties, including density and surface tension, in sodium chloride solutions at varying concentrations. Notably, these optimized models replicate experimental surface tensions at high ionic strengths, a property that is not well-captured by the ions of the original model in the SPICA-FF. The optimized unsolvated model also proves to be successful in reproducing experimental osmotic pressure. Additionally, the newly re-parameterized ion models capture hydrophobic interactions within sodium chloride solutions and shows qualitative agreement when modeling structural changes in phospholipid bilayers, aligning with experimental observations. For aqueous solutions, these optimized models promise a more precise representation of ion behavior.

P–32

SAXS-guided structural determination of PTPN4

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PTPN4 belongs to the non-receptor protein tyrosine phosphatase (PTP) family and consists of a N-terminal FERM domain, a PDZ (PSD-95/Dlg/ZO-1) domain and a C-terminal catalytic tyrosine phosphatase (PTP) domain. PTPN4 is involved in various biological activities such as T-cell signaling, learning, spatial memory and cerebellar synaptic plasticity. The cleavage of the phosphatase in the cell leads to the enzyme activation and the active form contains the PDZ and PTP domains that are connected by a linker. But, due to the disorder nature of this linker, the joined structure of PTPN4, is not yet determined. It has been shown that the PDZ domain inhibits the catalytic activity of the PTP domain, while the binding of a ligand to PDZ releases the auto-inhibition and activates the phosphatase [1]. However, the detailed mechanism of the PDZ domain for modulating the phosphatase is not yet fully understood. One possible approach to tackle such a problem, is to integrate experimental data into Molecular Dynamics (MD) simulations. Metainference is a Bayesian inference approach that integrates experimental data with prior distribution of models, while considering the effects of conformational averaging and errors. On the other hand, it has been shown that metainference can be combined with metadynamics to accelerate the exploration of conformational space [2]. We recently proposed a Bayesian model for automatic weighting of SAXS data combined with MD simulations, in order to find an optimal structural ensemble for PTPN4 [3]. Starting from this structural ensemble, we carried out extensive metainference metadynamics hybrid-resolution SAXS-driven MD simulations in the absence and presence of the ligand. For each system, we performed multi-replica simulations for 500 ns, leading to 100 μs of simulation time. This study allowed us to elucidate the functional dynamics of the PTPN4 and better understand the molecular mechanisms that control the catalytic activity of phosphatase.

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P–33

Substrate egress pathways in heme dependent tyrosine hydroxylase

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The L-tyrosine hydroxylase from Streptomyces sclerotialus (ssTyrH) is a heme-containing enzyme involved in the natural production of L-DOPA from L-Tyrosine (L-Tyr). This unique enzyme family distinguishes it from other L-DOPA synthesizing non-heme enzymes, in the presence of heme and hydrogen peroxide to catalyze this reaction. Due to its high specificity against L-Tyr, ssTyrH provides an environmentally friendly method for producing biomelanin. Nevertheless, to take real advantage of this enzyme family, further insights into its catalytic mechanism need to be elucidated. Specifically, in this study we have inspected the nature of the substrate's access to the catalytic site aiming to gain an understanding of which are the key residues involved in substrate migration. For this purpose, we utilized the random acceleration molecular dynamics (RAMD) method, steered molecular dynamics (SMD) simulations, and adaptive biasing force (ABF) simulation to investigate the egress pathways of the natural substrate from the ssTyrH catalytic site. Our findings revealed two primary pathways for L-Tyr to exit. Additionally, we observed multiple competitive exit pathways for hydrogen peroxide, both in the presence and absence of the substrate. This theoretical exploration offers insights into the mechanism of substrate migration, potentially aiding in the engineering of the enzyme to enhance or restrict access to this site.

P–34

The Role of Contiguous Hydrophobicity and Non-Aliphatic Hydrophobic Residues in Coevolution

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We have recently presented a sequence-based algorithm for detecting intrinsic modularity in proteins ("blobulation") and demonstrated its predictive power in conformational clustering of intrinsically disordered proteins [1]. In particular, we found that regions of contiguous hydrophobicity ("hydrophobic blobs") were likely to form tertiary interactions even in the absence of structure. This result suggests an approach for "ultra coarse-graining" protein sequences using monomers that each represent a varying number of residues. However, the significance of interactions between certain "specialty" hydrophobic residues, as well as the role of the local sequence in stabilizing such interactions, remains unclear. Identification of coevolving residues allows for a sequence-based approach to detecting residue-residue interactions using aligned protein sequences and phylogenies. Here, we test whether coevolving residues are more likely to be found in hydrophobic blobs, and whether the non-aliphatic hydrophobic residues in those blobs are particularly likely to be coevolving. We find that coevolving residue pairs are enriched for the case that both residues are found in hydrophobic blobs or both in polar blobs, and for pairs of "specialty" hydrophobic residues. These results suggest that ultra-coarse-grained models of complex polymers should consider not just the overall hydrophobicity and/or net charge of each monomer, but the number of residues that participate in specific attractive interactions.

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P–35

Thermo-responsive polypeptides: insights from polymer physics

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This paper will also be presented as a Young Researcher Talk, see that section for the abstract.

P–36

Towards an Automated Pipeline for Glycoprotein Simulations in Martini Coarse-grained Model

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Most proteins undergo a modification where complex sugar molecules, known as glycans, are covalently attached. This modification influences how proteins interact and function. Glycans exhibit large conformational freedom, making them difficult subjects for structural biology studies and resulting in a poor understanding of their role in protein mechanics. Classical molecular dynamics simulations offer a method to examine how glycans affect proteins at ns-us time scales. Utilizing a coarse-grained (CG) framework such as Martini 2 and 3 has been overwhelmingly successful in extending the time and spatial scales in biomolecular simulations, which is particularly important for glycoprotein studies. However, parameters for only a handful of common glycan species are present in Martini [1], [2], and a systematic approach for preparing a glycosylated system in CG is not yet clear.

In our work, we are aiming to develop a standardized pipeline to prepare glycosylated protein systems in Martini simulations, including automated parametrization and glycan addition to protein models. By using the GlycoSHIELD glycan library [3] as an atomistic reference and conformer selection tool, we aim to rapidly generate and validate CG glycan models, while providing clash-free starting structures. Here, we start with introducing simple modifications such as O-Mannosylation and O-GlcNAcylation into the martinize-vermouth tool and preparing glycoproteins for simulations in Martini 2 model as a test case. By using rescaled Lennard-Jones parameters we ensure correct glycan interactions [4]. Our proposed pipeline is expected to be versatile in preparing a wide range of glycosylated system in CG simulations, including Martini 3 framework.

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Towards an understanding of Turbo Grignard reagents: structural information from AIMD studies

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Main group organometallic reagents constitute today a critical asset for the synthesis of a broad range of valuable compounds, finding daily applications in academy and industry. Recently, bimetallic formulations arising from the combination of Li salts with these compounds have gained considerable attention for their ability to yield exceptionally powerful reagents, as exemplified by the Turbo Grignard - the enhanced version of one of the most prominent functionalisation tools in organic synthesis [1]. Compared to pure Grignard reactants, the metallation promoted by Turbo Grignards (RMgX•LiCl) proceeds selectively, with high-group tolerance and in high-yields [2]. Despite the success of these bimetallic formulations, the current understanding of the origin of the beneficial association with Li salts remains rather unsatisfactory, so far attributed to unidentified synergistic effects between the two metals. In our group, we recently used ab initio molecular dynamics (AIMD) coupled to enhanced sampling techniques to determine the mechanism of the Grignard reaction at its molecular level in THF [3,4]. Here, we used the same approach to characterise the structure of LiCl in solution and its interaction with Grignard reagents. [5] Nonetheless, AIMD studies reveal a vast conformational space associated with these systems, hindering comprehensive characterization due to the high computational cost associated with AIMD simulations. To address this challenge, we propose the integration of machine learning potentials (MLPs) for pushing molecular dynamics simulations. We show that a MLP trained on an extensive set of AIMD data effectively alleviates size and time limits, reproducing and predicting results of comparable quality.

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P–38

Towards the mechanistic understanding of a muscle protein kinase with multiscale molecular dynamics simulations

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Protein kinases of the titin-like family located in muscle fibers are postulated to act as mechanosensors. They are suggested to perceive the muscle sarcomere's mechanical stretch and trigger signal pathways in response. However, the exact mechanism of the mechanosensor activity of these protein kinases is not fully understood. In this project, we are working towards the mechanistic understanding of one of these muscle protein kinases. The molecular structure of the kinase makes the intramolecular domain-domain interaction particularly worthy of investigation.

Multiscale molecular dynamics simulations can provide valuable information about such a system on suitable time scales. We performed initial coarse-grained simulations from which we developed a customized analysis approach to study the domain-domain interactions of the protein kinase. This gave us first insights into the interaction landscape of the domains of the kinase and a good starting point for extended sampling on an atomistic scale. Therefore the application of a suitable backmapping protocol is needed, which we are currently focusing on.

P–39

Understanding heparin - calcium cation interactions: potential of mean force parametrization for the SUGRES coarse-grained model

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Glycosaminoglycans (GAGs) are biologically important polysaccharides, essential in the functioning of extracellular matrix. Their interactions with proteins impact many biochemical processes. As they are highly negatively charged, their binding is often mediated by solvent molecules or cations [1]. In addition to high charge density, flexibility and variable length make experimental studies of GAGs difficult, while simulations employing all-atom force fields are limited to short fragments [2].

Coarse-grained models of biomolecules have been developed to decrease the computational costs of biochemical simulations. SUGRES is one model designed for polysaccharides [3], which has recently been adapted for heparin [4] – an important GAG used in medicine as an anticoagulant. This work aims to introduce heparin interactions with calcium cations to the force field, as the negative charge of heparin makes them important in its biological function. To this end, we performed quantum chemical energy calculations of systems containing one of the two heparin monosaccharide subunits with a calcium cation in different positions. From their results, we derived potentials of mean force for the interaction and fitted analytical expressions for energy terms, which will be used in the SUGRES force field.

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P–40

Unique lipid-protein interaction fingerprints for the Kv7 ion channels

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Electrical signalling between cells is a fundamental biological mechanism regulated by ion channels. Kv7 is one such family of ion channels that conducts potassium ion efflux in response to a depolarization of the transmembrane potential. Five isoforms termed Kv7.1 to Kv7.5 makeup this family of ion channels and are distributed across a range of tissues where they perform a multitude of physiological roles. This includes Kv7.1 channels in the heart, Kv7.2 and Kv7.3 in the brain, Kv7.4 in the ear and Kv7.5 in smooth muscles. As such, loss of function in Kv7 channels contributes to serious disorders including long-QT syndrome, epilepsy, deafness, and loss of bladder control. A growing body of research points to the importance of membrane composition for Kv7 channel function. Certain lipids including cholesterol and fatty acids appear to exert differential effects on Kv7 channels. Understanding this phenomenon could be the key to developing drugs that selectively target specific Kv7 channels and minimise off-target effects. To achieve this, we first create AlphaFold models of Kv7.3 and Kv7.5 for which no structures currently exist. Then, we conduct coarse grained molecular dynamics simulations of all five Kv7 channel isoforms, totalling to 750 microseconds. The simulations were conducted in a complex plasma membrane model consisting of 63 unique lipid species. Analysis will be focused on revealing putative similarities and differences between the Kv7 channels in their interactions with lipids and influences on membrane biophysics. These constitute unique fingerprints which should aid in the development of lipid-memetic drugs that target Kv7 channel subtypes.

P–41

Unveiling the Phase Separation Behavior of Ultrashort peptides using UNRES coarse-grain force field

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The significance of protein phase separation in physiological and pathological processes is becoming increasingly evident. The liquid-liquid phase separation (LLPS) of proteins plays a crucial role in the formation of membraneless compartments in cells[1], but aberrant LLPS and liquid-solid phase separation (LSPS) can lead to the formation of neurotoxic aggregates[2,3]. Understanding the sequence determinants and molecular mechanisms underlying phase separation is vital for designing therapeutic targets to address protein-aggregation disorders.

In this study, we investigated the phase separation of many peptides, with chain length from 2 to 7 residues, using the UNRES coarse-grain force field. Each simulated system consisted of 320 peptide molecules. The size of the simulation box was adjusted so that in each simulation there was the same volume per amino acid residue. Through Multiplexed-Replica Exchange Molecular Dynamics(MREMD) simulations, we found that various peptides spontaneously phase separate into solid- or liquid-like condensates. Our predictions were verified through transmission electron microscopy(TEM). This study marks the successful prediction of the LLPS behavior of peptides, which has been challenging to investigate using existing theoretical and computational methods designed for larger proteins. Our findings shed light on the minimalistic building blocks and sequence determinants crucial for protein phase separation, offering new insights into the design of therapeutic strategies targeting protein-aggregation disorders.

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P–42

eBDIMS2: an efficient coarse-grained simulation algorithm to discover transition pathways and intermediate states of large proteins

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Proteins are dynamical macromolecules that often cycle between different conformations to achieve biological function. Trapping different protein conformational states is of paramount importance to get mechanistic insights into the protein biological behavior. Computational approaches – especially those that make use of coarse-grained (CG) models – can be of tremendous help to grasp the mechanistic basis of large-scale conformational changes [1-4]. One of such CG methods is eBDIMS, a technique based on elastic network models (ENMs) and Langevin dynamics that generates smooth transition pathways between the protein end states and is able to predict the structures of known intermediates [5,6]. In the Protein Data Bank, we currently find plenty of high-quality structural data on large proteins (> 3k residues), which have been trapped in different conformations during cryoEM experiments. Interestingly, these systems are also found to undergo large-scale motions. Yet, the majority of CG path-sampling methods available in the literature is unable to simulate conformational changes for such large systems. This limits our capability to decipher the conformational diversity in large proteins. For this purpose, we have developed eBDIMS2, an improved version of eBDIMS that can predict the transition pathways of gigantic proteins (up to 20k residues) in feasible computational times on standard computer workstations. We have recently investigated a variety of large systems, that are also relevant for cancer and other diseases, e.g., DNA-dependent protein kinase catalytic subunit (3k residues), neurofibromin (5k), ITP-receptor 3 (8k), ryanodine receptor (15k), fatty acid synthase ($\tilde{2}$1k), etc. By projecting our transition pathways on the low-dimensionality space of the experimental Principal Components [5,6], we can shed new light on the essential motions and the molecular mechanisms of these large and underexplored systems. Moreover, our simulated intermediate conformations can be used to generate atomistic seeds for Molecular Dynamics (MD), opening new possibilities to enhance the sampling of the conformational landscapes.

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