The ISQBP President’s Meeting 2021

29 June - 1 July 2021
organized from Strasbourg, France
Scientific committee
Annick Dejaegere, University of Strasbourg
Nathalie Reuter, University of Bergen Norway
Roland H. Stote, CNRS

Local committee
Sandra Bour, Myriam Rebetez and Philippe Verley, IGBMC

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<td>Opening comments</td>
<td>Roland H. Stote, IGBMC, CNRS - France</td>
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<td>16:15</td>
<td>Free-Energy Calculations Guide Drug Discovery for SARS-CoV-2</td>
<td>William Jorgensen, Department of Chemistry, Yale University - United States</td>
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<td>16:45</td>
<td>Molecular elucidation of the antibiotic resistance mechanism of New Delhi metallo-β-lactamase 1</td>
<td>Alessio Prunotto, Institute of Bioengineering, École Polytechnique Fédérale de Lausanne, and Department of Oncology, Ludwig Institute for Cancer Research, University of Lausanne - Switzerland</td>
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<td>The structure, dynamics and chloride conductance of WT and mutant CFTR as gleaned from MD simulations</td>
<td>Hanoch Senderowitz, Department of Chemistry, Bar-Ilan University - Israel</td>
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<td>17:30</td>
<td>Structural analysis of the interaction between the SARS-CoV-2 Spike protein and the human ACE2 receptor and druggable pockets identification to inhibit the SARS-CoV-2 viral entry</td>
<td>Mariem Ghoula, Unité de Biologie Fonctionnelle et Adaptative -- INSERM U1133, CNRS UMR 8251, Université de Paris - France</td>
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<tr>
<td>17:45</td>
<td>Gilda Loew Award Lecture</td>
<td>Studies of ion channel activation and modulation using computational approaches</td>
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<td>Carmen Domene, Department of Chemistry, University of Bath - United Kingdom</td>
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<td>18:30</td>
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<td>18:30</td>
<td>Break, Poster and Networking session</td>
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<td>20:00</td>
<td>Path sampling methodology for membrane permeability simulations</td>
<td>Ana Ghysels, IBiTech - Biommeda Group, Ghent University - Belgium</td>
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<td>20:15</td>
<td>Accelerated Molecular Dynamics to Explore Binding of Transition Metals to Amyloid-β</td>
<td>Jamie Platt, School of Chemistry, Cardiff University - United Kingdom</td>
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<td>Alzheimer’s is an Autoimmune Disease: An In Silico Study</td>
<td>Don Weaver, Krembil Brain Institute, University of Toronto - Canada</td>
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<td>21:00</td>
<td>Modelling the Peculiar Reactivity of the Molecular Chaperone Trap1</td>
<td>Stefano Serapian, University of Pavia - Italy</td>
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<td>21:15</td>
<td>Syk association with immune receptors, a unique entropy-driven mechanism to regulate protein interactions by phosphorylation</td>
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<td>Carol Post, Purdue University, West Lafayette, IN - United States</td>
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<td>16:00</td>
<td>Multiscale simulation for chemical biology: from enzyme evolution to interactive drug design in virtual reality</td>
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<td>Adrian Mulholland, Centre for Computational Chemistry, School of Chemistry, University of Bristol - United Kingdom</td>
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<tr>
<td>16:30</td>
<td>Biodegrading plastic and other mechanistic studies</td>
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<td>Maria Ramos, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade do Porto - Portugal</td>
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<tr>
<td>17:15</td>
<td>Moving pictures: Reassessing docking experiments with a dynamic view of protein interfaces</td>
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<td>Sophie Sacquin-Mora, Laboratoire Biochimie Théorique CNRS UPR9080 (LBT) – CNRS – IBPC - France</td>
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<td>17:30</td>
<td>Computational Biology Award Lecture</td>
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<td>CHARMM Additive and Drude Polarizable Force Fields: The Long and Winding Road....to....Hey Jude</td>
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<td>Alex MacKerell, Computer-Aided Drug Design Center, Department of Pharmaceutical Sciences, School of Pharmacy, University of Maryland - United States</td>
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<tr>
<td>18:00</td>
<td>Break, Poster and Networking session</td>
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<tr>
<td>19:45</td>
<td>Component Thermodynamics in Phase Separations</td>
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<td>Montgomery Pettitt, The University of Texas Medical Branch - United States</td>
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<td>20:15</td>
<td>Challenges in Protein Sequencing using 2-D MoS2 Nanopores : Answers from all-atom Molecular Dynamics</td>
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<td>Adrien Nicolaï, Laboratoire Interdisciplinaire Carnot de Bourgogne (ICB), UMR 6303 CNRS - Université de Bourgogne Franche-Comté - France</td>
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<td>20:30</td>
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<tr>
<td>20:45</td>
<td>Nanocapsule Designs for Antimicrobial Resistance</td>
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<td>Franca Fraternali, Randall Centre for Cell and Molecular Biophysics, King’s College London - United Kingdom</td>
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<td>21:15</td>
<td>High-throughput free energy methods for ligand discovery and design using multi-site λ-dynamics</td>
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<td>Charles L. Brooks, III, Departments of Chemistry and Biophysics, University of Michigan - United States</td>
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<td>Simulating epigenetic variants of DNA</td>
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<td>Modesto Orozco, University of Barcelona - Spain</td>
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<td>16:30</td>
<td>Recent successes in the simulation of nucleic acid structures</td>
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<td>Thomas E. Cheatham, University of Utah - United States</td>
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<tr>
<td>17:15</td>
<td>Pause</td>
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<tr>
<td>17:30</td>
<td><strong>Simulations of hERG PAS Domain</strong></td>
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<td><em>Lennart Nilsson, Karolinska Institutet - Sweden</em></td>
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<tr>
<td>18:00</td>
<td><strong>An Asymmetric Mechanism in a Symmetric Molecular Machine</strong></td>
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<td><em>Marco Cechinni, Institut de Chimie de Strasbourg – UMR7177 – University of Strasbourg - France</em></td>
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<td>18:30</td>
<td>Break, Poster and Networking session</td>
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<td><strong>Enhanced Antibody-Fc Receptor Interactions Revealed by Antibody Glycoengineering and Replica Exchange Simulations</strong></td>
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<td><em>Gene Chong, University of Maryland Baltimore - United States</em></td>
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<td>20:15</td>
<td><strong>Breaths, twists, and turns of atomistic nucleosomes with or without interaction partners</strong></td>
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<td><em>Vlad Cojocaru, Hubrecht Institute - Netherlands</em></td>
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<td>20:30</td>
<td><strong>Antibodies exhibit multiple paratope states influencing VH–VL domain orientations</strong></td>
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<td><em>Klaus Liedl, University of Innsbruck - Austria</em></td>
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<td>21:00</td>
<td>Closing comments</td>
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¹ The program is based on the Strasbourg local time (UTC+2) 

Posters will be accessible outside of session hours over the course of the meeting.
Investigations of immune stimulatory single stranded DNA by biomolecular simulations and NMR, Barna Tóth [et al.]

Homo- and heterodimers bHLH transcription factors induce different deformation of supercoiled DNA: a potential transcriptional regulation mechanism, Johanna Hörberg [et al.]

Deeprank-GNN: A Graph Neural Network Framework to Learn Interaction Patterns from Protein-Protein Interfaces, Manon Réau [et al.]

Accurate receptor-ligand binding free energies from QM conformational chemical space sampling, Matthias Stein [et al.]

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Pomarici [et al.]


Development of the Site-Identification by Ligand Competitive Saturation (SILCS) Methodology for Targeting RNAs with Small-molecules, Abhishek A. Kognole [et al.]

The importance of 29RAPRKKG35 linker region for HIV-1 virion structure and infectivity: a molecular dynamic study, Nadjoua Drici

A single-point mutation in the aminoglycoside-regulated riboswitch affects its dynamics and activity, Piotr Chyży [et al.]

AGIST for All, Johannes Kraml [et al.]

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**Poster Presentations June 30, 2021**

Thermosensitive Hydration – Solvation Entropy Determines Conformational Ensemble, Patrick K. Quoika [et al.]

Amino acids intercalated into bioinorganic clays: molecular understanding of binding modes in an nanoconfined aqueous environment, Vishal Kumar Porwal [et al.]

Étude des propriétés dynamiques et des interactions du domaine effecteur (dimère) de la protéine NS1 du virus de l’influenza A, Sarah Naceri [et al.]

Path sampling methods for protein-ligand binding kinetics, Wouter Vervust [et al.]

Structural analysis and conformational rearrangement of the human Insulin Degrading Enzyme, Mariem Ghoula [et al.]

Evaluation of AutoDock and AutoDock Vina on the CASF-2013 benchmark, Thomas Gaillard

Molecular dynamics simulations of hydrophobic gating in the TMEM175 channel: the effect of polarisability and water model, Charlotte Lynch [et al.]

DNA packaging in bacteriophages: The effect of DNA – capsid interactions, Cecilia Bores [et al.]

Investigating Ion-Exchange Adsorption of Proteins through Experiments and Molecular Dynamics Simulations, Marine Tournois [et al.]

Characterizing Immunoglobulin Inter-Domain Orientations, Valentin Hoerschinger

Surprisingly Fast Interface and Elbow Angle Dynamics of Antigen-Binding Fragments, Katharina Kroell [et al.]

Molecular dynamics as a supporting tool for refinement of the new MC4R Cryo-EM active structure, Fabrizio Fierro [et al.]
The simulation of amyloid-beta (Aβ) aggregation considering in vivo conditions, Hebah Fatafta [et al.]

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Application of molecular dynamics to elucidation of the mechanism of glucose net and exchange transport via GLUT1, Saul Gonzalez [et al.]

Differential electrostatic properties of reaction model as a tool for prediction and reverse design of catalytic properties, Pawel Kedzierski [et al.]

Towards the elucidation of a glucocorticoid and mineralocorticoid receptor ligand binding domain common dimerization interface, Laurent Blanchetti [et al.]

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Speakers ISQBP President’s meeting 2021

William Jorgensen * 1

1 Department of Chemistry, Yale University – United States

Free-energy calculations have had a revolutionary effect on computational chemistry. In conjunction with molecular dynamics and Monte Carlo simulations, they have enabled the calculation of free energy changes for wide-ranging phenomena including fundamental solution thermodynamics, activation barriers for reactions in solution, host-guest binding, and drug lead optimization. An overview of our FEP efforts leading to recent discoveries of extraordinarily potent inhibitors of the main protease of SARS-CoV-2 will be presented.

*Speaker
Molecular elucidation of the antibiotic resistance mechanism of New Delhi metallo-β-lactamase 1

Alessio Prunotto∗1,2, Guillermo Bahr3, Carolina Lopez3, Lisandro Gonzalez3, Alejandro Vila3, Matteo Dal Peraro1

1 Institute of Bioengineering, École Polytechnique Fédérale de Lausanne – Switzerland
2 Department of Oncology, Ludwig Institute for Cancer Research, University of Lausanne – Switzerland
3 Instituto de Biología Molecular y Celular de Rosario – Argentina

Antibiotic resistance constitutes a major threat to global health: the World Health Organization predicts that multi-resistant bacteria will cause up to 10 millions deaths per year within 2050, unless concrete action is taken. It is therefore crucially important to exploit the molecular mechanisms that bacterial evolution has developed to resist to antibiotic molecules: this knowledge could potentially inspire novel strategies to restore the efficacy of current treatments, and drive the discovery of new generations of antibiotics.

New Delhi Metallo-β-Lactamase 1 (NDM-1) is a bacterial metallo-enzyme which confers resistance towards last-resort antibiotics. Its fast and large geographical spread (16 alleles spanning over 70 countries) makes NDM-1 a major concern to global health. NDM-1 presents a catalytic site with two zinc ions that can hydrolyze, hence inactivate, antibiotic molecules. When a bacterial infection occurs, one of the typical immunitary responses of the organism is represented by metal starvation: when zinc ions are retrieved from the active site, metallo-β-lactamases are unable to perform their action against antibiotics. However, NDM-1 is resistant to metal starvation: this ability has been linked to a post-translational modification (lipidation) which anchors the enzyme to the bacterial membrane.

We investigated the molecular interaction between NDM-1 and the bacterial membrane through a combined computational and experimental approach: the results highlight an enhanced ability of the membrane-anchored NDM-1 to be excreted into vesicles, unlike other enzymes of the same class. The higher excretion contributes to spread the enzymatic action of NDM-1 through the whole infection site, and could explain its resistance towards metal starvation. Our analysis also highlighted that the globular domain of NDM-1 is tuned to interact specifically with the outer bacterial membrane: thanks to this molecular information, we developed a protocol to predict which other bacterial enzymes can potentially develop the same resistance mechanism.

Moreover, we found that the membrane-anchoring phenomenon is mainly mediated by cardiolipins and we identified the NDM-1 residues that drive the interaction with these lipids: these residues constitute a promising target for novel therapeutic strategies, as mutagenesis experiments suggest that inhibiting the interaction between these residues and cardiolipins significantly reduces the membrane-anchoring effect.

∗Speaker
The structure, dynamics and chloride conductance of WT and mutant CFTR as gleaned from MD simulations

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Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) is a transmembrane chloride channel implicated in the genetic disease Cystic Fibrosis (CF). For decades the 3D structure of the protein resisted all crystallization efforts mainly due to its instability outside its natural membrane environment. However, recent advances in cryo-EM techniques afforded several structures of hCFTR in different conformations along the protein’s gating cycle. These structures, while only representing snapshots of the highly dynamic and allosteric protein, provide excellent starting points for molecular simulations which could provide insight into CFTR’s structure, energetics, and dynamics under near-physiological conditions. Here we describe a series of such simulations with the ultimate goal of revealing the mode of action of CF-causing mutations. This information might prove useful for the development of new CF therapies. First, we demonstrate that a favorable correlation between experimentally determined thermostability data and calculated DDG values for various NBD1 (the first nucleotide-binding domain of the protein and a hotspot for CF-causing mutations) constructs is achievable by using the FoldX algorithm or by analyzing fluctuation profiles available from MD simulations. This allowed us to predict the effect on protein stability of several CF-causing mutations and to hypothesize on their mechanism of action. Next, we subjected several constructs of the full-length protein bearing other CF-causing mutations to a series of computational studies including lengthy MD simulations and molecular docking. These studies were performed on both apo-state CFTR and on CFTR constructs in complex with FDA-approved CFTR modulators bound to putative binding sites. Analysis of the results demonstrated that these studies could provide insight into the effect of CF-causing mutations on the structure and dynamics of CFTR in agreement with experimental findings. Finally, we subjected the full-length wild-type protein to 1 ms computational electrophysiology simulations, observing, for the first time the unbiased passage of chloride ions through the channel.

*Speaker
Structural analysis of the interaction between the SARS-CoV-2 Spike protein and the human ACE2 receptor and druggable pockets identification to inhibit the SARS-CoV-2 viral entry

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The year 2020 has been marked by the emergence of the highly pathogenic coronavirus SARS-CoV-2. SARS-CoV-2 has been rapidly and internationally spreading causing a serious global public health emergency, hence the importance of developing new drugs to inhibit the virus mechanism and to reduce global infection. The Spike protein, which is the key element for SARS-CoV-2 viral attachment, fusion and entry, is the main target for the development of antibodies, entry inhibitors and vaccines. The Receptor Binding Domain (RBD), which is located on the S1 subunit of the Spike protein, mediates viral entry through the Angiotensin Converting Enzyme 2 (ACE2) recognition. To develop anti-viral therapeutics for SARS-CoV-2, it is important to identify the amino acids stabilizing the SARS-CoV-2 RBD and ACE2 complex and to target specific regions of the complex in order to disrupt it. In this aim, we focused our work on the interaction between the RBD and ACE2 receptor complex. Two crystallographic structures (PDB IDs: 6M0J and 6LZG) were used to understand the interaction mechanism of both proteins. Then, the complex and the isolated RBD stability and flexibility were studied through Molecular Dynamics simulations with the GROMACS software. In total, we ran 40 simulations of 100ns each. The free binding energy of the complex and the identification of contributing key hot spots were done using the Molecular Mechanics Poisson-Boltzmann Surface Area (MM/PBSA) method. An extensive pocket search using the PockDrug software was also conducted to detect druggable pockets at the RBD surface. Altogether, our study helped us to identify interesting druggable pockets comprising crucial key residues for the RBD-ACE2 interaction and that can be targeted by efficient inhibitors that could potentially prevent the virus infection. Moreover, it has shown us the impact of the new emerging mutations (K417N, N501T, E484K) and the understanding of their molecular mechanisms in the most worrying SARS-CoV-2 variants like those in the UK, South-Africa and Brazil.
Studies of ion channel activation and modulation using computational approaches

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Ion channels are ubiquitous membrane-embedded transport proteins crucial for life. The central function of ion channels lies on their ability to selectively transport ions given the appropriate stimuli e.g. voltage, mechanical force, temperature or pH, and provided their regulatory gates are open. Gating mechanisms can be further modulated by ligands, a fact consistent with the fine tuning of their activity to molecular cues and organism demands. In this talk, by selected examples from our work, I will provide an overview of the current knowledge we have about activation, permeation and selectivity of ion channels and I will describe some of the technical challenges we face to model ion channels using atomistic computer simulation.
Path sampling methodology for membrane permeability simulations

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Permeability is a key property of biological membranes. Several strategies have emerged to predict membrane permeability from molecular dynamics (MD) simulations. The counting method uses the number of membrane crossings in a long conventional unbiased molecular dynamics simulation, which might lack sufficient statistics when the membrane forms a large free energy well or barrier (1). Alternatively, the widespread inhomogeneous solubility-diffusion (ISD) model can be used, which assumes purely diffusive kinetics. A methodology based on the Smoluchowsky equation was derived to extract the dynamics of oxygen permeation from these trajectories using Bayesian analysis (BA) (2). The results of the methodology are the free energy across the membrane, and the diffusion profiles normal and parallel to the membrane surface, from which the permeability and the characteristic entrance, transit, and escape times of permeants as well as characteristic lengths have been derived. The described BA methodology has the advantage that radial diffusion can be analyzed. However, for a hydrophobic molecule like water, both the counting method and the BA methodology are confronted with convergence issues. Therefore we now present new methodologies for cases with poor statistics on the permeation events, such as a water molecule permeating through an lipid raft (3). One methodology is based on accelerated MD simulation but is limited to purely diffusive permeation. The other method is based on a divide-and-conquer strategy that can assess the exact kinetics of the permeation event, i.e. without assuming diffusive kinetics in the membrane, by extending the path sampling methodology.


*Speaker
Accelerated Molecular Dynamics to Explore Binding of Transition Metals to Amyloid-β

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We report accelerated molecular dynamics simulation of amyloid-β (Aβ) peptide of 16, 28, 40 and 42 residues and their complexes with Cu(II), Fe(II), Zn(II). We show that the anchoring effect of metal ions reduces size and flexibility of all peptides, an effect that stems largely from restricted mobility of N-terminal Asp and His residues. Complexes with Zn(II) and Fe(II) show remarkable similarity, whereas that with Cu(II) exhibits properties closer to those of the free peptide. All metals are found to reduce helical character compared to the free peptide, including but not solely in the N-terminus where metal ions bind. Disruption to the pattern of salt bridges due to metal binding is also observed. Free energy surfaces extracted from accelerated MD are used to identify structural properties that are altered on metal binding.

*Speaker
Alzheimer’s is an Autoimmune Disease: An In Silico Study

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Alzheimer’s disease (AD), characterized pathologically by immunotoxic microglial activation and neurotoxic protein misfolding of β-amyloid (Aβ) and tau, is a fundamental disorder of human memory and information processing. The cause and cure of AD remain unknown. We report a series of in silico studies showing that AD is a brain-centric autoimmune disorder caused when Aβ, functioning as a cytokine, inflicts an accidental misdirected attack upon host neurons, yielding neuronal death by necrosis; membrane breakdown products from these necrotic neurons then elicit further Aβ release culminating in a chronic, self-perpetuating disease process. To enable the design of disease modifying therapeutics for AD necessitates understanding this combined proteopathic-immunopathic pathogenesis at an explicit molecular mechanistic level. To explore the initial stages of Aβ deposition on membranes, we performed a series of molecular dynamics simulations of Aβ misfolding adjacent to a membrane. These calculations, employing dipalmitylphosphatidylcholine bilayers, demonstrated pH-dependent attachment of helical Aβ to the membrane via its cationic N-terminal (Aβ5-16), electrostatically anchored by the HHQK domain (Aβ13-16), with subsequent intramembranous insertion of the lipophilic C-terminal (Aβ28-42), a process facilitated by cholesterol rafts. Inserting polyanionic glycosaminoglycans (GAGs; e.g. polysulfated heparin fragments) or gangliosides (GM1; monosialotetrahexosylganglioside) into the membrane improved the electrostatic binding of HHQK. Focussed B3LYP density functional theory calculations showed that the inclusion of transition metal cations (Cu2+) further strengthens the HHQK-GAG interaction, acting as a chelating bridge between "soft" histidine imidazole nitrogen atoms and "hard" GAG sulphate anions. Additional simulations showed that Aβ monomers could oligomerize prior to insertion, forming membrane disrupting oligomers. Control studies with scrambled Aβ revealed no membrane insertion. Next, we completed an in silico screen of 2,950 natural products to identify compounds capable of energetically favourable interactions to at least two of the HHQK residues; high ranking hits were obtained from plant-based phenylalanine metabolites constituting a potential drug-like molecular platform.
Modelling the Peculiar Reactivity of the Molecular Chaperone Trap1

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In this communication I will present an atomistic in silico model able to explain the peculiar reactivity of the (homodimeric) mitochondrial chaperone Trap1. This molecular machine-whose activity and/or expression levels are notably altered in several cancers(1)-oversees the correct folding of bound "client" proteins, a feat which it achieves through extensive conformational rearrangement.(2) Kickstarting this rearrangement are two strictly sequential ATP hydrolyses, which can only occur once the chaperone adopts a distinctively asymmetric "closed" state (Figure 1; left):(2) intriguingly, the ATP molecule bound to the buckled protomer Buc is cleaved first (and, even so, sluggishly); conversely, the straight protomer Str remains catalytically inert until the first hydrolysis has triggered its own buckling.

Using a previously tested recipe,(3) classical molecular dynamics (MD) proved that, in Str, nucleophilic water WatNuc is more frequently sequestered, via tighter hydrogen bonds, by a (conserved) tyrosine and its vicinal water WatTyr: "reactive poses" are thus more frequent in Buc. Hybrid semiempirical quantum-classical (QM/MM) MD with umbrella sampling, thoroughly benchmarked with density functional theory cluster models at the B3LYP-D3(BJ)/6-31+G(d,p) level, thence confirmed that looser WatNuc sequestration is enough to lower the free energy required for hydrolysis.

The model is thus able to justify Buc's greater reactivity, and shows that the conserved Tyr106 is an important ‘hotspot’ that allosteric Trap1 modulators should (indirectly) target.

REFERENCES

Syk association with immune receptors, a unique entropy-driven mechanism to regulate protein interactions by phosphorylation

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Spleen tyrosine kinase (Syk) is an essential player in immunity through its ability to couple a variety of membrane immunoreceptors to intracellular signaling pathways in an immune response. Receptor activation leads to the recruitment of Syk to a phosphorylated cytoplasmic region of the receptors called ITAM. Syk associates with high-affinity (nanomolar Kd) to the receptor ITAM, but the binding affinity decreases substantially (micromolar Kd) when Tyr 130 is phosphorylated. High-affinity binding results from bifunctional binding of two SH2 domains of Syk that are spatially well oriented by an intervening linker domain to fit two phosphotyrosines of ITAM. The decreased affinity for Syk association with immune receptor by Y130 phosphorylation is a unique allosteric mechanism driven by an increased entropy penalty from conformational disorder in the SH2–SH2 inter-domain structure, while SH2-ITAM binding contacts are not affected, and binding enthalpy is unchanged. To begin to understand how phosphorylation triggers disorder without affecting binding interactions, we used molecular dynamics simulations of unphosphorylated and phosphorylated Syk to characterize conformational equilibrium of interdomain structure of the two forms. The results of the simulations will be described in this talk. We find disparate electrostatic networks involving highly conserved charged residues at the domain interfaces. Differences between unphosphorylated and phosphorylated Syk in the number of residues and the lifetime of connectivities of the network are observed. The simulated behavior is consistent with NMR relaxation measurements, giving confidence in the microscopic characterization provided by MD. We discovered the key factor to be a triad of charged residues that is centrally located between the three domain and anchors both networks.
Multiscale simulation for chemical biology: from enzyme evolution to interactive drug design in virtual reality

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Simulations are revealing detailed mechanisms of biomolecular systems and functionally relevant dynamics, and contributing to enzyme design. Biomolecular simulations can be used as computational ‘assays’ of biological activity, e.g. to predict drug resistance or the effects of mutation. Molecular simulation methods of various types are now capable of modelling processes ranging from biochemical reactions to membrane dynamics, and offer increasing predictive power. Recently, this has included identifying key features of SARS-CoV-2 proteins. Molecular dynamics (MD) simulations on long timescales can model substrate binding, and reveal dynamical changes associated with thermoadaptation and directed evolution of enzyme catalytic activity. MD simulations can calculate thermodynamic properties such as activation heat capacities. Increasingly, simulations are contributing to the design and engineering of natural enzymes and de novo biocatalysts. Interactive MD simulation in virtual reality allows direct manipulation of biological macromolecules, going beyond mere visualization to allow e.g. fully flexible docking of drugs into protein targets such as the SARS-CoV-2 main protease. Groups of researchers can work together in the same virtual environment. Mechanisms of signal transduction in receptors can be studied by a combination of equilibrium and nonequilibrium MD simulations, e.g. identifying a general mechanism of signal propagation in nicotinic acetylcholine receptors. Different types of application (e.g. ranging from chemical reactions to signal transduction) require different levels of treatment, which can be combined in multiscale models to tackle a range of time- and length-scales, e.g. to study drug metabolism by cytochrome P450 enzymes combining coarse-grained and atomistic MD and QM/MM methods. By coupling together different levels of description, multiscale methods can address e.g. how chemical changes in individual molecules cause changes at larger scales. QM/MM methods are an archetype of multiscale methods in biochemistry and can be used for modelling transition states and reaction intermediates, to identify catalytic interactions, and to analyse determinants of reactivity. QM/MM modelling can identify mechanisms of covalent inhibition and predict the activity of bacterial enzymes against antibiotics.

References


*Speaker


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Biodegrading plastic and other mechanistic studies

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Plastics have become essential to modern society, driven by their amazing versatility coupled with low production costs. However, due to their resistance to natural degradation, the long lifespan of plastics represents a global environmental problem, posing a serious and growing risk to flora and fauna, and even more so to marine ecosystems. The fact that our current recycling efforts still lack sustainability is also a problem. Fortunately, as a possible response to the accumulation of plastics in the biosphere, microbes are adapting to this situation by developing enzymes and catabolic pathways capable of partially degrading man-made plastics. Recently, the bacterial strain *Ideonella sakaiensis* 201-F6 was shown to be able to grow on low-crystallinity films of polyethylene terephthalate (PET), one of the most commercialized plastics, widely used in packaging and textiles. Two of this bacterium’s enzymes, PETase and MHETase, which specifically degrade PET into its natural components, offer promising starting points for synthetic biology and process engineering to help solve the current environmental threat. Using this recent knowledge, we aim to develop a novel technology to biodegrade PET on a large scale. To do this, we begin by establishing the mechanisms of the PETase and MHETase reactions in the same way that we have been doing in the last few years of our research. (1-4) This talk aims at the development and progress concerning the biodegradation of PET.

*Speaker*
Moving pictures: Reassessing docking experiments with a dynamic view of protein interfaces

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The modeling of protein assemblies at the atomic level remains a central issue in structural biology, as protein interactions play a key role in numerous cellular processes. This problem is traditionally addressed using docking tools, where the quality of the models is based on their similarity to a single reference experimental structure. However, using a static reference does not take into account the dynamic quality of the protein interface. Here, we used all-atom classical Molecular Dynamics simulations to investigate the stability of the reference interface for three complexes that previously served as targets in the CAPRI competition. For each one of these targets, we also ran MD simulations for ten models that are distributed over the High, Medium and Acceptable accuracy categories. To assess the quality of these models from a dynamic perspective, we set up new criteria which take into account the stability of the reference experimental protein interface. We show that, when the protein interfaces are allowed to evolve along time, the original ranking based on the static CAPRI criteria no longer holds as over 50% of the docking models undergo a category change (which can be either toward a better or a lower accuracy group) when reassessing their quality using dynamic information.

*Speaker
CHARMM Additive and Drude Polarizable Force Fields: The Long and Winding Road....to....Hey Jude

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Empirical force field development represents a tedious, time-consuming effort to solve a typically underdetermined problem. My involvement in the additive CHARMM force field began in 1986 motivated by the need to produce self-consistent parameters allowing for the first simulation of a nucleic acid-protein complex, targeting the protein ribonuclease T1. Following this initiation into force field optimization, in 1988 I become involved in the development of the all-atom additive CHARMM force field, ultimately becoming the de facto leader of CHARMM force field development efforts. This highly collaborative effort led to the creation of the additive CHARMM36 biomolecular force field including the CHARMM General Force Field (CGenFF). While development of the additive force field continues to this day, in 2000 work on a polarizable force field based on the classical Drude Oscillator model was undertaken. These ongoing efforts have yielded a comprehensive, computationally accessible polarizable biomolecular force field with currents efforts including development of a Drude General Force Field (DGenFF) and extensions and additional optimization of the biomolecular aspects of the model. In the talk I will try and present too many details in too little time as an analogy to our approach to force field development over the last 35 years.
Component Thermodynamics in Phase Separations

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We use the properties of peptides and proteins in water at varying concentrations in order to understand the structural and thermodynamic changes that occur during aggregation. Aggregation often manifests as a liquid-liquid, phase separation at the solubility limit. Thermodynamic signatures of this aggregation of short peptides is remarkably similar to the thermodynamics of folding or collapse of longer peptides in water. Disorder structures are found experimentally to preferentially be in intracellular condensates. We decompose the free energy and study the conformational entropic contributions. We find enthalpy-entropy compensation between the components in the phase separated systems give mechanistic hypotheses.
Challenges in Protein Sequencing using 2-D MoS2 Nanopores: Answers from all-atom Molecular Dynamics

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Solid-state nanopores (SSN) made of 2-D materials such as molybdenum disulfide (MoS2) have emerged as one of the most versatile sensors for single-molecule detection. One of the most promising applications of SSN is DNA and protein sequencing, at a low cost and faster than the current standard methods. The detection principle relies on measuring the relatively small variations of ionic current as charged biomolecules immersed in an electrolyte traverse the nanopore, in response to an external voltage applied across the membrane (1). The passage of a biomolecule through the pore yields information about its structure and chemical properties, as demonstrated experimentally particularly for DNA molecules. Indeed, protein sequencing using SSN remains highly challenging since the protein ensemble is far more complex than the DNA one. In the present work, we focus on challenges in protein sequencing using 2-D MoS2 nanopores. Three challenges are highlighted using all-atom Non-Equilibrium Molecular Dynamics to simulate protein translocation experiments through MoS2 nanopores. First, the threading of the protein through the nanopore is discussed (2). Second, the modification of the nanopore dimensions in order to slow down the passage of the protein through the pore is detailed (2). Finally, the application of time series analysis tools in order to identify protein sequence motif from measured raw data is presented (3).


*Speaker
Nanocapsule Designs for Antimicrobial Resistance

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Antimicrobial resistance and drug delivery have been main focuses of the recent medical research. Recently engineered virus-like nanocapsules derived from synthetic multi branched peptides have been shown to promote bacterial membrane poration and to be suitable for gene delivery at the same time [1]. The atomistic details of the nanocapsule assembly, necessary for the antimicrobial and gene delivery activities, are not accessible to experimental techniques. Therefore, the nanocapsule stability in water and its interaction with a model membrane was studied through Molecular Dynamics simulations, comparing the results with the available experimental data [2]. Integrated results from simulations at different resolutions highlighted the role of the amphiphilic structure of capzip as driven promoter of the assembly stability. Moreover, simulations highlighted a strong affinity with a bacterial model membrane and lower with a mammalian one.

This investigation shows the essential role of computational techniques in rationalizing the experimental results and suggests how to manipulate capzip composition in order to trigger particular functions [3]. The quick disruption of the membrane observed in the simulations after the insertion event correlates well with the experimental findings. Further simulations on a model mammal membrane show much weaker interaction: the composition of the membrane, which does not host negatively charged peptides, makes the binding unfavourable, explaining the low levels of cytotoxicity observed for the nanocapsules.


Left: designed configuration of the antimicrobial pseudocapsule in solution. Right top: AFM profile of capsules of Supported Lipid Bilayers and simulation of a capsule on a model bacterial membrane.

$^*$Speaker
membrane. Right bottom: AFM in time of a pseudocapsule converting into a pore on Supported Lipid Bilayers.
High-throughput free energy methods for ligand discovery and design using multi-site \( \lambda \)-dynamics

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Multi-site \( \lambda \)-dynamics (MS\( \lambda \)D) provides a high-throughput framework for rigorous free energy calculations. In this talk we will review applications of this approach to a broad range of receptor and ligand pairs illustrating the precision, accuracy and high-throughput nature of free energy calculations carried out with MS\( \lambda \)D. We will illustrate how different estimators of the free energy differences can provide excellent estimates of free energy differences for multiple ligands simultaneously.
Simulating epigenetic variants of DNA

Modesto Orozco * 1

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DNA force-fields have reached a level of accuracy that allows predictive power in the calculations. In particular I will summarize how atomistic MD simulations can decipher a physical code imprinted into the epigenetic fingerprint of mammal cells. By combining a variety of theoretical calculations and experimental techniques I will discuss how methylation and hydroxymethylation changes the properties of DNA and this in turn modifies chromatin structure and then gene function.
Recent successes in the simulation of nucleic acid structures

Thomas Cheatham

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Although Professor Cheatham is usually talking about problems with force fields and about issues with sampling limitations in large scale simulations of nucleic acids, in this ISQBP presentation he will be talking about recent successes. This includes the observation of spontaneous drug intercalation in unbiased simulations, spontaneous Hoogsteen base pair formation in DNA duplexes consistent with measurements from NMR relaxation, and recognition of riboflavin as a stabilizer of oxo-G modified G-DNA when bound to an abasic site. He will also highlight current status of the nucleic acid force fields and, if time, outline where we hope to be going in terms of accurately modeling nucleic acid structures.
Simulations of hERG PAS Domain

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The human *ether-à-go-go* related gene (hERG1) is a voltage-gated potassium channel (Kv11.1). Inherited mutations in KCNH2, the gene which encodes Kv11.1 channels, can result in long QT syndrome type 2 (LQTS2), an electrical disorder of the heart associated with sudden cardiac death. Many such mutations have been documented in databases, but less often has an attempt at a structural interpretation been made. Understanding how biological structure relates to disease is of fundamental importance in medicine in order to derive therapeutic remedies. Several disease related mutations have been describe in the PAS (sensor) domain of the hERG protein. In this work perform molecular dynamics simulations of both the wild-type PAS domain, and the novel deletion mutation Y43 which is reported for the first time and is associated with syncope and LQT2 syndrome. It is hoped that molecular modeling may yield molecular-level insights as to how congenital mutations cause LQT2 syndrome.

*Speaker
An Asymmetric Mechanism in a Symmetric Molecular Machine

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The design of molecular architectures exhibiting functional motions is a promising area for disruptive technological development. Towards this goal, rotaxanes and catenanes, which undergo relative motions of their sub-units in response to external stimuli, are prime candidates. Here, we report on the computational analysis of the contraction/extension of a bistable [c2]daisy chain rotaxane. Using free energy calculations and transition path optimizations, we explore the free energy landscape governing the functional motions of a prototypical molecular machine with atomic resolution. The calculations reveal a sequential mechanism in which the asynchronous gliding of each ring is preferred over the concerted movement. Analysis of the underlying free energy surface indicates that the formation of partially rearranged intermediates entails crossing of much smaller barriers. Our findings illustrate an important design principle for molecular machines, namely that efficient exploitation of thermal fluctuations may be realized by breaking down the large-scale functional motions into smaller steps.

*Speaker
Enhanced Antibody-Fc Receptor Interactions Revealed by Antibody Glycoengineering and Replica Exchange Simulations

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Glycans on the antibody Fc fragment can be modified to enhance binding to Fc receptors (FcRs) and stimulate immune-cell activity. For example, the removal of core fucose in Fc glycans has been shown to improve cytotoxic activity in natural killer cells for applications in cancer immunotherapy. In this work, we use molecular dynamics simulations with enhanced sampling methods-specifically, Hamiltonian replica exchange with solute tempering and biasing potentials (HREST-BP)-to reveal the critical glycan-protein and glycan-glycan interactions that enhance the binding affinity between the antibody Fc and FcR upon removal of core fucose in the Fc glycan. We also demonstrate that modifying the polarity of the C6 functional group in core fucose can enhance Fc-FcR binding and highlight these mechanisms to modulate the immune response.
Breaths, twists, and turns of atomistic nucleosomes with or without interaction partners

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Nuclear chromatin is a highly dynamic structure made of arrays of nucleosomes with different sizes and degrees of compaction. Structural rearrangements in chromatin are essential for gene regulation, are hallmarks of cell fate transitions and are based on inter and intra nucleosome dynamics. Therefore, understanding these rearrangements requires elucidating nucleosome structural flexibility and the and how different factors affect it. In the nucleosome, 145-147 base pairs of DNA are wrapped around an octamer of histone proteins, each unique histone occurring twice. The mechanisms of intra nucleosome dynamics, especially in native nucleosomes with genomic sequences remain elusive. I will present our recent efforts in studying structural dynamics of nucleosome and the structural basis for the nucleosome recognition by pioneer transcription factors. These special transcription factors bind to sequence specific sites on DNA wrapped in nucleosomes and contribute to chromatin opening directly or indirectly. To date, little is known about the structural mechanisms involved in their interaction with genomic nucleosomes. From ~25µs of atomistic molecular dynamics simulations we found how the interplay of two histone tails modulate the breathing of genomic nucleosomes. In addition, from experiments and additional ~25µs simulations we revealed how the pioneer factor Oct4, a master regulator of stem cell pluripotency, interprets and enhances structural flexibility of nucleosomes bound during the conversion of somatic cells into pluripotent stem cells. I will discuss the state-of-the-art and challenges in simulating nucleosomes and chromatin substructures at atomistic resolution.

References


*Speaker
Antibodies exhibit multiple paratope states influencing VH–VL domain orientations

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In the last decades, antibodies have emerged as one of the most important and successful classes of biopharmaceuticals. The highest variability and diversity of an antibody is concentrated on six hypervariable loops, also known as complementarity determining regions (CDRs) shaping the antigen-binding site, the paratope. Whereas it was assumed that certain sequences can only adopt a limited set of backbone conformations, in this study we present a kinetic classification of several paratope states in solution. Using molecular dynamics simulations in combination with experimental structural information we capture the involved conformational transitions between different canonical clusters and additional dominant solution structures occurring in the micro- to millisecond timescale. Furthermore, we observe a strong correlation of CDR loop movements. Another important aspect when characterizing different paratope states is the relative VH/VL orientation and the influence of the distinct CDR loop states on the VH/VL interface. Conformational rearrangements of the CDR loops do not only have an effect on the relative VH/VL orientations, but also influence in some cases the elbow-angle dynamics and shift the respective distributions. Thus, our results show that antibodies exist as several interconverting paratope states, each contributing to the antibody’s properties.

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Poster Abstracts ISQBP President’s meeting 2021
Investigations of immune stimulatory single stranded DNA by biomolecular simulations and NMR

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Immunotherapies require novel type of delivery systems with specifically tailored adjuvants to activate immune responses. Among immune stimulators of microbial origin, oligodeoxynucleotides (ODNs) represent the most advanced potential adjuvants. ODNs are unmethylated single stranded DNA (ssDNA) sequences with CpG-motifs, which are able to activate the innate immune system by binding to TLR9 receptors. Adjuvant effects are optimized by maintaining ODNs and vaccine antigens in close proximity, which can be achieved by loading the immune stimulator and the antigen cargo to an appropriate carrier such as inorganic nanoparticles.

Immobilisation of ODN immune stimulators onto the surface of nanoparticles while maintaining multivalent presentation to TLR9 receptors requires knowledge of their conformational properties. De novo modelling of ssDNA conformation, opposed to that of double stranded DNA, is challenging due to multiple reasons. ssDNA lacks stable structures and can only be described as an ensemble of interconverting conformations, thus methods for adequate sampling of the conformational space need to be applied. Force fields for simulation of DNAs were, however, developed by testing them mainly on duplex DNA and their ability to reproduce conformations of ssDNA is unclear. In this regard, modelling of ssDNA likely face similar challenges as modelling of Intrinsically Disordered Proteins.

We set out to test the accuracy of existing DNA force fields using atomistic molecular dynamics (MD) simulations and NMR spectroscopy. Translational diffusion coefficients were obtained from diffusion experiments and compared to translational diffusion coefficients, radius of gyration and end-to-end distances calculated from MD simulations. Furthermore, we analysed secondary structure formation and descriptors of dynamic behaviour. Outcome of comparisons for different DNA force fields are discussed.

*Speaker
Homo- and heterodimers bHLH transcription factors induce different deformation of supercoiled DNA: a potential transcriptional regulation mechanism

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DNA transcription is fundamental for the conversion of genetic information into RNA, which later translates into proteins. In eukaryotes, DNA transcription is primarily regulated at the initiation stage, when one or several collaborative transcription factors (TFs) locate and specifically bind short stretches of non-coding DNA, known as "response elements", located in the vicinity of a gene. Homologous TFs often exhibit specificity towards identical response elements (2-3) – yet they bind different genomic sites, recruit different collaborative TFs, and regulate different transcriptional pathways. One of the mechanisms, which can explain the differential regulatory behaviours of homologous TFs, can include variations in their response to DNA supercoiling – the key regulatory forces of eukaryotic transcription. Here we address computationally how three homologous human basic-helix-loop-helix (BHLH) heterodimers/homodimers: MycMax, MadMax and MaxMax bound to the E-box-containing sequence ‘GGCGAGTAGCACGTGCTACTCGC’ respond to changes in DNA supercoiling. We use all-atomic microsecond long molecular dynamics (MD) simulations together with an in-house developed torsional restraint that controls the total helical twist of DNA molecule without affecting any other structural parameter. We apply the torsional restraint to the E-box response element and the four adjacent flanking nucleotides on both sides, and gradually over- and underwind the DNA fragment by 0.5°/bp step to a maximum of ±5°/bp step. Consistent with our previous findings for the Basic-leucin-zipper (BZIP) family, the binding of a BHLH factor makes DNA more torsionally rigid. The three BHLH-DNA complexes exhibit similar torsional rigidity, however, in the presence of torsional stress, the BHLH factors allosterically deform DNA in a different fashion. These results make us hypothesize that homologous TFs contribute to differential regulatory transcriptional responses by exploiting the torsional stress deformation energy of a supercoiling wave to recruit different collaborative TFs or to manipulate distal DNA topology.


*Speaker
Deeprank-GNN: A Graph Neural Network Framework to Learn Interaction Patterns from Protein-Protein Interfaces

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Protein-protein interactions (PPIs) are essential in all cellular processes of living organisms including cell growth, structure, communication, protection and death. Acquiring knowledge on PPI is fundamental to understand normal and altered physiological processes and propose solutions to restore them. In the past decades, a large number of PPI structures have been solved by experimental approaches (e.g., X-ray crystallography, nuclear magnetic resonance, cryogenic electron microscopy). Given the remarkable success of Convolutional Neural Network (CNN) in retrieving patterns in images, CNN architectures have been developed to learn interaction patterns in PPI interfaces.

We have developed Deeprank (https://github.com/DeepRank/deeprank), an open-source configurable deep learning framework for data mining PPIs using 3D-CNNs. Deeprank maps atomic and residue-level features from PPIs to 3D grids and applies 3D CNNs to learn problem-specific interaction patterns. Deeprank was applied to two problems: 1) the classification of biological vs. crystallographic PPIs, and 2) the scoring of models of protein-protein complexes generated by docking. Deeprank was shown to compete with- or outperform state-of-the-art methods in both scenarios.

CNNs however come with major limitations: First, they are sensitive to the input PPI orientation, and it may require data augmentation (i.e. multiple rotations of the input data) for the network to forget about the orientation in the learning process; second, the size of the 3D grid is unique for all input data, which does not reflect the variety in interface sizes observed in experimental structures and may be problematic for large interfaces that do not fit inside the predefined grid size. A solution to this problem is to use instead Graph Neural networks (GNN). By definition, graphs are non-structured geometric structures and do not hold orientation information. They are rotational invariant and can easily represent interfaces of varying sizes. We have therefore developed Deeprank-GNN that converts PPI interfaces into graphs and uses those to learn interaction patterns. We benchmarked the performance of Deeprank-GNN in scoring docking models from the CAPRI score set. Results show that it performs equally or outperforms state-of-the-art scoring functions (HADDOCK, Deeprank, DOVE, iScore) on 10/13 complexes. Deeprank-GNN is freely available from https://github.com/DeepRank/Deeprank-GNN/

*Speaker
Accurate receptor-ligand binding free energies from QM conformational chemical space sampling

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Non-covalent ligand-receptor interactions are a challenge to computational means in terms of accuracy and efficacy. An exhaustive sampling of possible binding modes plus a reliable calculation of receptor-ligand binding free energies is required. The conformational rotamer ensemble sampling tool (CREST) uses the GFN2-xTB Hamiltonian to calculate intermolecular interactions very efficiently. An iterative conformational sampling using meta-dynamics and normal molecular dynamics simulations gives a number of low energy structures that are thermally accessible. It is shown that this sequential workflow is able to sufficiently sample the chemical conformational space of ligand-receptor complexes from a recent challenge of host-guest non-covalent interactions. Subsequent refinement steps with tighter criteria and final calculations of ligand binding free energies give results in good agreement with experimental data for a drug molecules with a mean error of 3 kcal/mol. This shows that the CREST tool is able to generate reliable ligand binding poses in the receptor without a priori knowledge of possible modes of binding. The xTB energies of association are also supported by double-hybrid DFT calculations and demonstrate the reliability of the approach.

*Speaker
Insights into antibiotic breakdown by class D $\beta$-lactamases through multiscale simulations

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Using atomistic simulations, our research aims to elucidate mechanisms of antibiotic breakdown by $\beta$-lactamase enzymes. These enzymes are the main cause for resistance against $\beta$-lactam antibiotics, the oldest and most widely prescribed group of antibacterial drugs. OXA-48 $\beta$-lactamases in particular are globally widespread and frequently diagnosed as key players in multidrug resistant infections. They confer resistance against a variety of $\beta$-lactam antibiotics, most notably against "last resort" carbapenem drugs (with specific preference for imipenem). Enzyme variants within the OXA-48 family have distinctly different properties, and some have acquired activity against expanded-spectrum oxyimino cephalosporins (ceftazidime). However, it remains unclear, where enhanced activity against specific $\beta$-lactams originates.

Starting from experimentally determined enzyme crystal structures, we model $\beta$-lactam antibiotic inactivation by OXA-48s using combined quantum mechanics/molecular mechanics (QM/MM) simulations. The aim of our simulation protocols is to assay the activities for different enzyme-substrate conformations efficiently (keeping the required computational resources low), whilst correctly distinguishing between active and inhibited $\beta$-lactamases. This translates to employing semi-empirical methods with short sampling times in QM/MM umbrella sampling simulations. Deducting information from these simulations, we are able to rationalise the experimentally observed differences in antibiotic hydrolysis for cephalosporins and carbapenems. For cephalosporin (ceftazidime) inactivation, our computational protocol correctly differentiates between inhibited (OXA-48) and non-inhibited (OXA-163) enzymes. Further inspection reveals active site hydration to be a key factor in determining catalytic efficiency, as an increase in the number of water molecules around the catalytic base correlates with decreased reaction rates. For OXA-48 with carbapenem antibiotics, we confirm this effect, and further reveal the most catalytically competent substrate orientation. Subsequent comparison between the studied carbapenems (imipenem and meropenem) indicates that a change in the hydrogen bonding pattern between the substrate and active site water molecules is behind the higher efficiency of imipenem breakdown. Our simulations help dissecting the determinants of $\beta$-lactam breakdown on the molecular level, which complements experimental research and can provide predictions on the likely $\beta$-lactam susceptibility of new variants as well as suggestions for antibiotic design.

*Speaker
A Machine Learning Classifier to Select Water-Ligand Interactions to Facilitate Empirical Force Field Optimization

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Accurate empirical force fields (FF) allow for less computationally expensive molecular mechanical models of ligands to be used in place of quantum mechanical models for molecular dynamics simulations. Although FFs have become increasingly generalizable, they must be refined by optimizing parameters for each ligand. Most steps in the FF parametrization process have been automated by software such as FFParam, but manual input is still required during charge fitting. A function of FFParam is to automatically specify the orientation of water molecules interacting with a ligand as required for optimization of electrostatic parameters. However, water interaction input files generated by FFParam must be manually curated to delete files with secondary interactions between water and non-targeted atoms of the ligand, termed obstructed interactions, a time-consuming and inconsistent process. To resolve this issue, a supervised machine learning (ML)-based classifier program was developed in Octave to categorize input files. To train and test this program, water interaction input files were generated and manually classified for a group of 10 chemically diverse FDA-approved drugs. Half of the ligands were randomly selected to train the model while the others were used to test its performance. Training established decision boundary parameters to divide the interactions into two classes (verified, obstructed), based on the closest distance between the water and non-target atoms, the average van der Waals radii of the atoms involved in that interaction, and the manual classification of each water interaction. The program was able to correctly classify 87.6% of interactions in the testing set, similar to the 85.1% sorted correctly in the training set, meaning the model performs well on unfamiliar data. This similarity remained when the roles of the sets were reversed: 84.6% sorted correctly in the testing group and 87.1% in the training set. These results indicate that the ML model was successful in automatically classifying water interactions, a key step in charge fitting ligands during parametrization. Major benefits of the ML approach are its generalizability to various drug classes and the ease of retraining with a modified dataset.
Multiscale Simulations of Radical Cation Guanine in the Nucleosomal DNA

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All eukaryotic cells deal with the issue of tightly packing their genomes inside a small nucleus. This physical problem has been solved by the formation the chromatin.1 Eukaryotic DNA is organized into nucleosome which is the fundamental unit of chromatine and comprises 147 base pairs of DNA wrapped around an octameric core composed of four pairs of histone proteins (2 pairs of H3-H4 and two pairs of H2A, H2B).2,3 Histone protein cores have very flexible protuberant tails which play a pivotal and critical role in regulating many biological processes such as transcription, expression, and DNA repair.4 The intrinsically disordered nature of histone tails creates obstacle for the structure and dynamics investigations.1 Hereby, we simulate the four histone tails, isolated and with the presence of DNA using the palindromic alpha satellite sequence (from 1kx5 pdb structure). In addition to normal Molecular Dynamics simulations, we use Replica exchange with solute tempering (REST2) approach in order to increase the conformational sampling of the flexible tails. This method, which is an outstanding algorithm for a sampling of molecular dynamics,5 is ideal for the sampling of aqueous protein solutions in which there are large-scale solute conformational changes.6 Because of the intrinsically disordered character of the histone tails, we performed all simulations with two different well-established force fields for protein such as "traditional" amber force field ff14SB, and the IDP-specific force field ff14IDP.7 We report here a conformational analysis of histone tails to compare the behavior of histone different force fields. Furthermore, we consider different protonation states of histidine residues in the absence and presence of DNA. Further analyses consider post-translational modifications (PTMs) on the flexible N-terminal histone tails that include covalent modifications of specific amino acids, such as the methylation of lysines which plays a major role in epigenetic regulation.3 Our results will help us to determine the most consistent parameters and relevant starting points to perform nucleosome simulations.

*Speaker
Shark Antibody Variable Domains Rigidify Upon Affinity Maturation - Understanding the Potential of Shark Immunoglobulins as Therapeutics

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Modern Elasmobranchii – a subclass of cartilaginous fish including rays, skates and sharks – are known to be the first animals with canonical adaptive immune system. The fact that their antibodies had to evolve under extreme conditions led to the development of a particularly stable type of antibodies: the so-called Immunoglobulin New Antigen Receptors (IgNARs). The variable domains of these heavy chain only antibodies are functional as single domains, and despite their small size these antibodies are able to bind targeted antigens with an equally high specificity compared to conventional IgG-like antibodies. An affinity maturation pair of IgNAR antibody variable domains (VNARs), differing in a total of thirteen point mutations, was investigated. Crystal structures were available in complex with the Hen Egg-White Lysozyme, as well as without the antigen present.

By using enhanced sampling techniques, namely metadynamics, in combination with classical molecular dynamics simulations we could investigate the respective conformational spaces and reconstruct kinetic and thermodynamic properties of the binding interface. Thus, we noticed a substantial reduction of flexibility, as well as a reduction of the sampled conformational spaces and conclude a rigidification upon affinity maturation, which is accompanied by a shift of this conformation towards the structure capable of binding the antigen. Nevertheless, this binding competent conformation was observed with smaller state probabilities in the wildtype ensemble as well, indicating the conformational selection paradigm as binding mechanism. Moreover, the binding/unbinding pathway was reconstructed as a two-step binding mechanism.

The impact of the key residues involved in molecular recognitions were analyzed in detail by performing interaction analysis. Thereby we identified critical amino acids, which contribute most to the stabilization of the individual variants and to antigen binding. Being small in size and having a high stability, VNAR domains are of huge interest for the pharmaceutical industry as therapeutic antibodies. Nevertheless, for the understanding of such proteins and for their development and design, their dynamic nature cannot be neglected.

*Speaker
Implicit Solvent Model for the Polarizable Drude Force Field and its application for pKa prediction

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Induced electronic polarization may be important for many biological processes including proton binding to titratable residues in proteins. We have developed a continuum Poisson-Boltzmann (PB) model coupled to the polarizable force field based on the classical Drude oscillator (1). The model was parametrized to reproduce experimental solvation free energies of a set of small molecules. The model reproduces well experimental solvation free energies of 70 molecules. To allow pKa calculations using Monte Carlo (MC) simulations and the Drude PB model, we further developed a new computational method (2). In this method, the most populated protonation states at the selected pH, corresponding to residues that are half-protonated at that pH, are sampled using the exact relative free energies, while an approximation for the protein polarization of low-populated protonation states is introduced. The highly populated protonation states used to compute the polarization and pK’a’s are then iteratively improved until convergence. It is shown that for lysozyme, when considering 9 of the 18 titratable residues, the new method converged within two iterations with computed pK’a’s differing only by 0.02 pH units from pK’a’s estimated with the exact approach. With the Drude PB, we obtain superior results to the additive CHARMM36 (C36) force field as demonstrated using pK’a’s of 94 titratable sidechains in 8 proteins. The RMS deviation between experimental and computed pK’a’s using the Drude-PB model is relatively insensitive to the choice of the internal dielectric constant in contrast to the results obtained with the additive C36 model. At the higher internal dielectric constant of 20, pK’a’s computed with the additive C36 model converge to the results obtained with the Drude polarizable force field. In addition, inclusion of both syn and anti orientations of the proton in the neutral state of acidic groups is shown to yield improved agreement with experiment. References:

*Speaker
How contribution of higher-order proximal distribution functions influence the solvent structure

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The proximal distribution function (pDF) systematically identifies the solvent structure around solutes from a knowledge of molecular distribution functions based on the proximity criterion as the key element. Previously, pDFs considered the contribution of the nearest neighbor distribution only. Here, the pDF reconstruction algorithm is extended to terms including next-nearest neighbor contribution as well. A variety of solute molecules (including alanine, butane, and propanol) are examined. Further, the analysis is extended to include the myoglobin P6 unit cell, in which 6 myoglobin proteins are fully packed. To justify the results, molecular dynamics (MD) simulations are performed and solvent number density distribution around the solute molecules are derived and compared with the results from the nearest+next-nearest neighbor pDF reconstruction model. It is shown that this modification improves the reconstruction of the solvent number density distribution in the near vicinity of solute molecules. Finally, it is shown that solute-solvent van der Waals (vdW) interaction energies are in fairly good agreement with the simulated values.
Conformational changes regulate the half-life of proteins of the Bcl-2 family

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Apoptosis is a natural process required for the removal of redundant cells during development, potentially dangerous cells and those in senescence. Cell death dysregulation has been implicated in a variety of human diseases such as cancer, neurodegenerative disorders, and autoimmunity. This process is regulated by several proteins among them, those belonging to the Bcl-2 family. Members of this family are grouped according to their participation in the apoptotic mitochondrial pathway in pro- and anti-apoptotic proteins. The members of this family are characterized by the Bcl-2 homology (BH) domains, BH1, BH2, BH3, BH4, as well as an intrinsically disordered region (IDR) depicted as "flexible loop domain" (FLD), and a transmembranal (TM) region that anchors mitochondrial outer membrane (MOM). The main core is formed by BH1, BH2 and BH3 domains that interact with BH3 domain of other family members. The interaction between pro-apoptotic and pro-survival proteins of Bcl-2 family exquisitely regulate cell death. The IDR regions are rich in PEST regions (proline (P), glutamic acid (E), serine (S) and threonine (T)). The two main degradation pathways mediated by protein PEST sites are degradation of ubiquitin-proteasome and cleavage of µ-calpain. Some studies report that the half-life for Bcl-2 is around 24 hours and for Bcl-2A1 it is 30 minutes2.

We perform molecular dynamics of the three-dimensional models of proteins Bcl-2 and Bcl-2A1, where we used the Gromacs software version 4.6 and OPLS-AA force field. The simulations were performed under NPT conditions for 100 ns. Here we show the result of simulations performed at 310 K. Here we performed a comparative analysis between Bcl2 and Bcl-2A1. We used of essential dynamics to identify global collective movements of proteins which are crucial for the regulation of biological activity. Our results indicate that these conformational changes in the Bcl-2 protein hide the regions where the PEST sites are located, avoiding the attack of proteases, while in the Bcl-2A1 protein the PEST regions remain exposed all the time. This could give an explanation of why the Bcl-2 protein has a much longer half-life than the Bcl-2A1

*Speaker
Ensembles in solution as a new paradigm for antibody structure prediction and design

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The ability of antibodies to specifically recognize a broad variety of antigens is determined by the antigen-binding fragment (Fab), in particular the variable fragment (Fv). The diversity of an antibody is concentrated on six hypervariable loops, forming the antigen-binding site, the paratope. Five of the six complementarity determining region (CDR) loops have been assigned to canonical structures, assuming that the loops can only adopt a limited number of main-chain conformations.

For decades CDR loops have been thought to be limited to static canonical conformations determining their binding properties. Here, we escape this paradigm of static canonical structures determining binding properties and specificity of antibodies.

In contrast to this static view of the binding interface show that antibodies exist as ensembles of paratope states. These paratope states are defined by a characteristic combination of CDR loop conformations, which interconvert into each other in the micro-to-millisecond timescale by correlated loop and interdomain rearrangements. We demonstrate that crystal packing effects can distort the paratope state and result in misleading X-ray structures. We achieve a complete description of conformations, thermodynamics and kinetics of the binding paratope in solution. We show that these findings do not only help to improve antibody structure prediction by identifying the dominant structure in solution, but we also find that docking profits substantially from reliable conformational ensembles. These findings have broad implications for antibody design and the development of biotherapeutics as they provide a new understanding of CDR loop states in antibody-antigen recognition and their dynamics.

*Speaker
Coarse-grained modelling of ionic and DNA transport through nanopores

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Nanopore Force Spectroscopy (NFS) experiments consist in applying an electric potential difference to guide a charged biopolymer through an artificial or protein nanopore, inserted in a solid or lipid membrane, in the presence of a salt solution. A macromolecule passing through the pore induces a decrease in the ionic current by partially blocking the pore, according to the nature of the molecule and the pore characteristics. The alpha-hemolysin toxin channel is widely used for NFS experiments, due to its commercial availability. This protein nanopore enables the passage of a single-stranded DNA and has been the subject of several DNA translocation and unzipping experiments in our lab. However, the theoretical understanding of the physical processes of these experiments is not straightforward, and microscopic information from molecular dynamics is greatly needed. Coarse-grained models are a good alternative to classical all-atom models since they enable longer simulations, closer to the experimental characteristic times.

Coarse-grained models are a good alternative to classical all-atom models since they enable longer simulations for large systems, closer to the experimental characteristic times. In collaboration with experimentalists of the lab, we performed coarse-grained molecular dynamics of the ionic transport through alpha-hemolysin, inserted into a lipid bilayer surrounded by solvent and ions, in the presence of several electric fields to mimic the electric potential difference, using the MARTINI coarse-grained force field. Our system, composed of around 400,000 atoms, is reduced at 90,000 coarse grains, allowing molecular dynamics of several microseconds, which is close to the characteristic times of the nanopore experiments. We were able to observe several specific features of this pore (current asymmetry and anion selectivity) in agreement with previous studies and experiments, and also identified the charged amino-acids responsible for these current behaviours. Moreover, we recently successfully performed steered molecular dynamics of the transport of a single-stranded DNA through alpha-hemolysin. These promising preliminary results with DNA are the first step to elucidate the mechanisms involved in DNA unzipping experiments.

*Speaker
Intermolecular Electrostatic Interactions in the Short Range: a Quantum Chemical Topology Analysis

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A correct description of electrostatic interactions is crucial in molecular modelling. The approximate treatment in terms of point charges or higher order multipoles leads to accurate results in the long range, but becomes troublesome in the short-range regime due to the so-called charge penetration (CP) error arising from the interpenetration of molecular charge densities. Different solutions have been proposed basing on additional damping functions that are parameterised against the electrostatic energy between unperturbed densities (1,2), as that provided by the symmetry-adapted perturbation theory (SAPT). SAPT is one of the many energy decomposition analyses (EDAs) available, that differentiate between energy terms in an intermolecular interaction. In contrast to SAPT and other orbital-based EDAs, a different perspective is taken under the real space interacting quantum atoms (IQA) method. IQA belongs to the quantum chemical topology realm and has been extensively used in many controversial bonding situations (3). With the aim of analysing and characterising short-range electrostatic interactions under this reference-free framework, we have studied both the S66 and the S66x8 datasets of non-covalent complexes by means of IQA along with the quantum theory of atoms in molecules (QTAIM). To provide a wider perspective of such interactions, the IQA energy terms have been compared with those provided by two commonly used FFs such as RESP and AMOEBA at both the molecular and atomic levels. We show how the IQA electrostatic pair term may become a good descriptor of binding in conjunction with D3 dispersion and how its behaviour parallels to a large extent that provided by other multipolar alternatives at the molecular level. However, at the atomic level the two FFs considered reveal inconsistent, whereas the QTAIM multipoles preserve their similarity with the IQA counterparts. As a final step, the CP error is inspected and a consistent definition à la IQA is presented relying on a combined partition of both space and charge densities, what ultimately highlights the main role played by intramolecular effects in the overall stabilisation found in CP corrections.

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The directional vinculin-actin catch-bond: a molecular mechanism of biomechanical properties under force

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Mechanotransduction refers to the processes by which a cell adapts its behavior in response to mechanical stimuli. It involves a cascade of highly complex biomolecular interactions and reactions. Single-molecule force-spectroscopy techniques provide exquisite tools to study some of these key processes. In particular, a directional catch-bond behavior has been evidenced for the vinculin-actin complex - at stake in the cytoskeleton by anchoring the F-actin to the membrane. The life-time of the complex has been shown to increase when actin is pulled towards its (-)-end while vinculin is immobilized. Yet, this mechanical behaviour is not straightforwardly understood experimentally, because of the relatively poor accessible observables. This work relies on molecular dynamics (MD) to give theoretical insights into the molecular understanding of this phenomenon. A special emphasis will be put on the modeling of the actin-vinculin complex, which involves biomolecular systems of significant size. The modeling of this proteinic complex under forces uses state-of-the-art all-atom MD techniques, including steered-MD simulations and enhanced sampling simulation schemes. On the one hand, conformational studies put into perspective the assumptions made based on recent structural data, such as the existence of a weak and strong binding state due to a helical rearrangement. On the other hand, steered-MD aims to bring decisive insights into the directionality of a possible catch-bond behaviour.

*Speaker
Ion and Water Interactions with a Biomimetic Nanopore: Molecular Dynamics with Effective Polarization

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Interactions of ions and water at hydrophobic interfaces are suggested to play a key role in biological anion transport. Recently, crystal structures of ion channels and transporter proteins have revealed that chloride ions may form favourable interactions with the hydrophobic sidechains. Molecular dynamics (MD) simulations have revealed that the surface affinity of halide ions to hydrophobic/water interfaces is affected by inclusion of polarisation. Non-polarizable (NP) force fields neglect electronic polarizability which overestimates the strength of interactions between interacting charges, whilst full polarisable force fields can capture electronic polarizability at the expense of computational efficiency. The electronic continuum correction (ECC) (Vazdar et al. (2012) J. Phys. Chem Lett 3:2087) is a computationally efficient mean-field approach for approximating the effects of polarisation by simply rescaling ionic charges in NP force fields. Here, we use MD simulations to investigate the behaviour of water, Na+ and Cl- ions within the hydrophobic region of a biomimetic model nanopore. The model nanopore was constructed by modifying a carbon nanotube and was designed to imitate the polar openings and hydrophobic regions of pentameric ligand-gated ion channels (pLGICs). Analysis of ion and water distributions relative to the hydrophobic nanopore walls were compared for simulations with and without ECC applied. Radial density profiles reveal a structured layer-by-layer distribution of ions and water, with Cl- ions exhibiting a preferential adsorption to the hydrophobic pore walls, comparable to effects seen at hydrophobic/water interfaces. Similar effects were observed for simulations of varying salt concentration and pore radius. These specific Cl- ion effects were only seen when using the ECC force field. Radial distribution functions (RDFs) were used to probe the solvation structure surrounding each ion and potential of mean force calculations (PMFs) have been used to calculate free energy landscapes of single ions permeating the pore. Our findings provide insight into the localisation of chloride ions to hydrophobic surfaces in nanopore geometries and contribute to our understanding of anion selectivity mechanisms in biological ion channels.

*Speaker
Structural and Conformational study of FMN-containing miniSOG

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In recent experimental studies (1), it has been demonstrated that certain flavins (such as FMN) and flavoproteins (FMN containing proteins such as miniSOG) have the ability to activate Pt(IV) prodrug complexes under hypoxic conditions and in the presence of electron donor species as NADH, to form therapeutically active Pt(II) complexes. Furthermore, selected mutations in miniSOG modulate this catalytic activity(2). In this work, molecular dynamic simulations and density functional theory calculations are used in order to analyze the structure of wild type and mutated miniSOG during the photoreduction process, and the role the flavin binding pocket might have in the latter. Additionally, bond analysis techniques as energy decomposition analysis and ETS-NOCV are used to rationalize the effect the protein residues might have in the catalytic properties of flavin. It is observed that the activity of the flavoprotein can be modulated by altering the binding pocket of the flavin and therefore its electrochemistry, and also by hindering the access to the FMN through the entrance channel.

References


*Speaker
Structural mechanism of Fab domain dissociation as a measure of interface stability

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In the latest years, monoclonal antibodies (mAbs) have emerged as new potential therapeutics for the treatment of several pathologies, as cancer or autoimmune diseases. They are proteins, commonly produced by our organism as a defense against pathogens, and they are composed by two light chains and two heavy chains. Their shape, similar to a Y, allows the simultaneous binding of two different antigens, as viruses, fungi, bacteria or others. In fact, each arm of the Y, also known as antigen binding fragments (Fab), can bind a pathogen, triggering the immune reaction against it. The Fab is composed by two constant domains (CH1-CL) and two variable domains (Fv), that interact with the antigen with 6 hypervariable loop that shape the Complementary Determining Region (CDR). Therapeutic antibodies should not only recognize antigens, but also need to be free from developability issues, such as poor stability. Thus, the mechanistical understanding and characterization of stability is a critical determinant for rational antibody design.

In this study, we use molecular dynamics simulations to investigate the melting process of sixteen antigen binding fragments (Fabs). Here, we propose two Fab dissociation mechanisms, showing a separation in the VH-VL or in the CH1-CL domains. We provide a detailed structural description of the dissociation mechanism and identify key interactions in the CDR loops that contribute to stabilization. Mechanistically, the dissociation of the VH-VL or CH1-CL domains can be represented by conformational changes in the tilt angles between the domains. These results can be further confirmed by Markov-state models which allow to characterize the Fab dissociation pathways kinetically and thermodynamically. In line with the experimental stability data, we observe a strong population shift from the native conformation towards the dissociated state upon decrease in stability. Our findings have broad implications in the development and design of new and more stable antigen binding fragments.

*Speaker
Solvation Thermodynamics in Ionic Solution: an Extension of Grid Inhomogeneous Solvation Theory Predicts Salting-Out Coefficients

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Hydration thermodynamics play a fundamental role in the pharmaceutical industry as well as in environmental research. Hydrophobicity of biopharmaceuticals leads to poor expression levels and stability, while membrane permeability of drugs depends on a balance of polar and apolar interactions. On the other hand, hydration determines the solubility of organic substances, which in turn affects their degradation, evaporation, and bioaccumulation. Numerous methods exist to predict solvation thermodynamics of compounds ranging from small molecules to large biomolecules. Recently, methods based on Inhomogeneous Solvation Theory (IST) have seen significant advances, with applications ranging from protein-ligand binding to membrane permeability of macrocycles. However, there has been no implementation of IST that can estimate solvation properties involving more than one solvent species. Here, we attempt to bridge this gap by presenting an extension to the Grid Inhomogeneous Solvation Theory (GIST) algorithm that can take salt contributions into account. We show the validity of our method by predicting a set of salting-out coefficients and compare its performance to Thermodynamic Integration (TI) calculations. The first-order solute-solvent entropy computed by GIST has only a small impact on the salting-out effect, while an estimate of the second order entropy is shown to significantly improve our predictions. We expect that our method will be a valuable tool to describe solvation thermodynamics in ionic solution.

*Speaker
Development of the Site-Identification by Ligand Competitive Saturation (SILCS) Methodology for Targeting RNAs with Small-molecules

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RNA molecules can act as potential drug targets in different diseases as their dysregulated expression or misfolding can alter various cellular processes. Non-coding RNAs account for ~70% of the human genome and these molecules can have complex tertiary structures that present a great opportunity to be targeted by small molecules. Until recently, the majority of structure-based drug discovery efforts have been focused on targeting proteins; however, with the advances in the field and with greater understanding of RNA structures and functions, it is now within our reach to transfer and apply computer-aided drug design methods from protein targets to RNA targets. Site Identification by Ligand Competitive Saturation (SILCS) is a unique computational approach that provides a comprehensive 3D characterization of a target macromolecule in the form of functional group affinity maps, termed grid free energy (GFE) FragMaps obtained through enhanced sampling simulations of the macromolecule in an aqueous solution containing a range of chemical probes. The GFE FragMaps can be used to dock small molecule ligands using SILCS-MC, a Monte-Carlo based algorithm, and predict their binding conformation as well as approximate binding affinities for the target. Here we report development of the SILCS and the SILCS-MC protocols to be applied to RNA targets, including 5 different RNA targets and their reported small molecule binding partners. The protocols take into account the highly negative charge on the polynucleotide and optimize the sampling of the hydrophobic, polar and charged probes around it. Promising initial results indicate that the SILCS-RNA approach may significantly enhance drug discovery efforts targeting RNAs with small molecules.

*Speaker
The importance of 29RAPRKKG35 linker region for HIV-1 virion structure and infectivity: a molecular dynamic study

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The critical role of the linker region made by the short basic sequence 29RAPRKKG35 for virion structure and infectivity has been previously outlined in many research papers. This well conserved peptide fragment located between the two Cys-His boxes of human immunodeficiency virus type 1 virus is of major interest due to its significant flexibility that seems to be the manner by which the Nucleocapsid P7 can interact with either single or double stranded nucleic acids. In this report, molecular dynamic simulations were conducted on the mutants R29S, A30P, P31L, R32G, and S3, that denotes the replacement of 32RKK34 by SSS of the NCp7’s 29RAPRKKG35 linker region. The structural behaviour of this short domain was examined theoretically in terms of RMSD, as well as hydrogen bond population established in each mutant. In silico site-directed mutagenesis performed on each motif of the linker region can provide us with a qualitative guideline for determining the impact of each mutation on the molecular events characterizing the in vitro viral infectivity investigated previously by Ottmann and co-workers (Ottmann, Gabus, & Darlix, 1995)
A single-point mutation in the aminoglycoside-regulated riboswitch affects its dynamics and activity

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Riboswitches are fragments of non-coding mRNAs with the ability to regulate gene expression upon binding ligands. Here, we investigate the dynamics of a synthetic 27-ribonucleotide long N1 riboswitch that binds various aminoglycosides including neomycin (1). The N1 riboswitch forms a hairpin with a bulge serving as the ligand-binding pocket that is stabilized by the apical loop. Experiments indicate that the A17G mutation in the N1 riboswitch reduces its activity 6-fold (2).

To examine the internal dynamics of the riboswitches, we applied generalized replica exchange with solute tempering (gREST), which allows extending the conformational sampling (3). Based on our simulation trajectories, we recorded a relationship between the reduced activity of the A17G riboswitch mutant and its dynamics. In the unbound state, we detected unique interactions within the ligand-binding nucleotides, not observed in the riboswitch without mutations. These interactions cause reorientation of the U8 nucleobase towards the riboswitch apical loop, which leads to the partial occupation of the aminoglycoside binding site. In addition, the presence of a triple stacking C6:U7:G17 interaction, characteristic only for the A17G mutant, prevents the riboswitch from opening the binding site for neomycin. Thus, the pool of conformations of the A17G mutant unfavorable for ligand binding is enriched with respect to the riboswitch without mutations. This mutation also changes the RNA conformation in the bound state, where the crucial C6:G17 stacking interaction, linking the bulge and apical loop responsible for the riboswitch regulatory activity, was weaker.

Overall, the A17G substitution changes the interaction network within the unbound riboswitch and affects the discovered conformational selection mechanism leading to neomycin binding. To examine the process of RNA-neomycin association, we currently optimize the replica exchange molecular dynamics simulations with umbrella sampling to determine the neomycin binding pathway. These simulations should explain the differences in the association path of neomycin to the riboswitch with and without the mutation.

*Speaker
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(1) Chyży et al., 2021, Front.Mol.Biosci., 8:633130;
(2) Weigand et al., 2008, RNA, 14:89-97;
Grid Inhomogeneous Solvation Theory (1, 2), short GIST, has been proven a very useful tool for the calculation of localized thermodynamic properties of water and for the description of surface hydrophobicity. GIST has been shown to be highly valuable in calculating hydrophobicity of binding pockets in serine proteases and in drug design by accounting for desolvation of binding interfaces. (3,4) In an effort to speed up the calculation, we reimplemented the code for the energy calculation on the GPU, resulting in superior computational performance. (3) Further, we improved the calculation of the entropy, by introducing a correction term for the six-integral entropy, as some preconditions on this term strongly depend on substantial amounts of sampling. Thus, by significantly accelerating the energy calculations and by providing a more accurate calculation of the entropy, we improved the underlying algorithm. We also generalized the algorithm so that it is applicable for all rigid solvent molecules. This version of the algorithm uses the center of mass instead of a center atom, which in itself is straightforward, but we further generalized the calculation of the orientation of the solvent molecules, i.e., the quaternion construction. Thus, we arrive at an easy way to calculate the orientational entropy for any rigid solvent molecule, making the GIST algorithm applicable for all rigid solvent molecules.

Thermosensitive Hydration – Solvation Entropy Determines Conformational Ensemble

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Thermosensitive polymers undergo a counter-intuitive phase transition with a lower critical solution temperature: they form a gel above a certain temperature, whereas they exist in liquid mixture with the solvent below this temperature. This phase transition is associated with a structural collapse of the polymer chains, i.e., the Coil-Globule transition, which links the dynamics of the system on a molecular level with the macroscopic solution properties. We investigated the conformational dynamics of a selection of acrylamide-based polymers – including thermosensitive and non-thermosensitive representatives – to understand the onset of this extraordinary phenomenon. To this end, we performed extensive molecular dynamics simulations over a wide range of temperatures (in total over 0.6 ms). We discovered the freely jointed chain model to successfully resolve different conformational states, where other established descriptors (such as the radius of gyration) failed. Therewith, we were able to accurately reconstruct the thermodynamics of the process at different temperatures, including the conformational entropy of the polymer. Finally, we identified the polymer-solvent interactions to be essential for the energetic balance of the transition, leading to the conclusion that different conformations exhibit largely different solvation properties. Specifically, we determined the entropy of solvation to be the decisive quantity for the thermosensitive Coil-Globule transition, which is an often overseen, yet important, contribution to the free energy of conformational rearrangements.

*Speaker
Amino acids intercalated into bioinorganic clays: molecular understanding of binding modes in ananoconfined aqueous environment

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Layered double hydroxides (LDH) are claylike materials in which planar inorganic surfaces are separated by an interlamellar space of nanometric size. Materials intercalating a wide range of anions can easily be synthesized,(1) leading to technological applications (from electrochemistry to the food industry), with a particular focus on biocompatible systems.(2) In addition, LDH can be used as a playground to investigate Bernal’s hypothesis(3), according to which mineral surfaces could provide a favorable environment for the origin of life on Earth. As a matter of fact, recent computational studies on such hybrid systems point out some fitting conditions for the formation of peptide bonds of intercalated amino acids (4, 5) and suggest that changes in the water content and the pH of the system can play a significant role on local interactions.(6) We shall present results obtained through a joint computational and experimental study applied to systems intercalating aspartate, glutamate, and succinate anions. Our analysis will point to some fundamental questions: What is the role of the amino group in determining the binding mode of the anion with the surface? Can the size of the side chain affect such binding mode for amino acids? How does water affect the local landscape, and, on the other hand, how is water affected by the nanoconfined environment and the presence of anions? To elucidate these points, we shall focus on MD simulations aimed at understanding the structure to (macroscopic) property relationship based on i) the nature of the intercalated anion and on ii) the hydration content following the experimental adsorption isotherm. A comparison with the experimental results will be provided as well as a presentation of some open questions.

References

*Speaker
Étude des propriétés dynamiques et des interactions du domaine effecteur (dimère) de la protéine NS1 du virus de l’influenza A

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Le virus Influenza A, constitue l’un des problèmes majeurs actuels de santé publique. Transmissible à l’Homme, il touche principalement les mammifères et les oiseaux. Il se distingue des autres types d’Influenza par son pouvoir pathogène potentiellement élevé. Actuellement, la recherche est très active sur la protéine non-structurale 1 (NS1), visant à trouver et à concevoir de nouvelles molécules synthétiques pouvant potentiellement cibler NS1 et inhiber sa fixation à l’ARN double brin et donc freiner, voire arrêter, le cycle viral induit par l’influenza A. NS1 est une petite protéine de 230 acides aminés organisée en dimère composée d’un domaine de liaison à l’ARN (RBD) et d’un domaine effecteur (ED), ces deux domaines sont reliés par une région non structurée très flexible appelée "linker". NS1 se lie à l’ARN (via son domaine RBD) et à différentes autres protéines (via son domaine ED). Des structures cristallographiques de NS1 ont révélé un polymorphisme de la structure quaternaire: le dimère NS1 peut adopter trois conformations distinctes (fermée, semi-ouverte et ouverte) en fonction de l’orientation des domaines EDs par rapport aux RBDs. Nous avons étudié les propriétés dynamique et d’interaction des domaines ED (dimères) à l’aide d’approches bio-informatiques permettant de simuler l’évolution temporelle d’un système moléculaire (simulations de dynamique moléculaire). Un modèle structuraux des trois formes du dimère NS1 ont été construites pour différentes souches virales grâce à l’approche computationnelle de modélisation par homologie basée sur la séquence de la souche H6N6 et en utilisant comme support structural les structures expérimentales du dimère NS1 entières disponibles dans la Protein Data Bank (PDB). L’effet du linker et des variations de séquence entre la souche H6N6 et la souche H5N1 (adoptant la forme ouverte) sur la stabilité de chaque modèle a été mis en évidence dans l’objectif de développer une thérapie indépendante de la souche. L’étude structurelle de NS1 et l’identification des surfaces d’interaction du domaine ED ainsi que l’étude de la stabilité des contacts ED-ED et RBD-ED au cours de la dynamique nous ont permis de mieux comprendre les propriétés dynamique de la protéine NS1 et de mettre en évidence son importance en tant que cible thérapeutique pour la lutte contre l’Influenza A.

*Speaker
Path sampling methods for protein-ligand binding kinetics

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In this study, state-of-the-art molecular dynamics simulation techniques are used to extract the binding kinetics of protein-ligand complexes. Kinetic parameters, such as the (un)binding rate constants and residence time, have recently been shown to be important for predicting the in vivo efficacy of candidate drug molecules. Computational tools to predict binding kinetics are therefore needed in the screening stage of the drug-design pipeline, where the combination of thermodynamic and kinetic selectivity results in better drug candidates. However, the time-dependent nature of kinetics makes it a challenging subject for current computational resources.

Replica Exchange Transition Interface Sampling (RETIS) (1) is an exact path sampling method. RETIS uses an initial trajectory to generate new trajectories using shooting moves, which are accepted or rejected according to the Metropolis-Hastings algorithm. RETIS allows paths to be exchanged between different path ensembles, which greatly enhances the sampling efficiency. This is a promising feature to tackle the known challenge of orthogonal degrees of freedom (DoFs), where a user-defined, low-dimensional reaction coordinate misses important free energy contributions in these orthogonal DoFs, resulting in inaccurate kinetics. RETIS is in principle reaction-coordinate independent and requires only the definition of an order parameter that distinguishes between the bound and unbound states of the protein-ligand complex. RETIS delivers reactive trajectories with the true dynamics (i.e. no bias potential is used), which also allows to extract qualitative information of the (un)binding process.

The method is currently set up for the ABL-imatinib complex. ABL is a kinase protein important for cell regulation, and imatinib is the first-line drug for patients with chronic myeloid leukemia, where the fusion oncoprotein BCR-ABL renders the ABL kinase domain in a constitutively active state. In the future, we envision to extend the methodology to general protein-ligand complexes.


*Speaker
Structural analysis and conformational rearrangement of the human Insulin Degrading Enzyme

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Insulin Degrading Enzyme (IDE) is a metallopeptidase that degrades a large panel of amyloidogenic peptides and is thought to be a potential therapeutic target for type-2 diabetes and neurogenerative diseases like Alzheimer’s disease. Interestingly, IDE is a cryptidase. Its catalytic chamber, known as a crypt, is formed so that peptides can be enclosed and degraded. However, the molecular mechanism of IDE function and peptide recognition remains elusive. It has been shown that IDE undergoes several conformational changes and switches between closed and open states in order to regulate peptide degradation and cleavage. Thereby, it is essential to unfold IDE mechanism and provide more information on how conformational dynamics can modulate the catalytic cycle of IDE.

In this aim, a free-substrate IDE crystallographic structure (PDB ID: 2JG4) was used to build a complete structure of IDE with the MODELLER software. IDE stability and flexibility were studied through Molecular Dynamics simulations with the GROMACS software and the CHARMM36m force field. In total, we ran 7 simulations of 1 microsecond each to cover a wide range of the IDE conformational space. The crypt volume as well as the Solvent Accessible Surface Area (SASA) were calculated to witness IDE conformational dynamics switching from a closed to an open state. The Gibbs free energy landscapes were also investigated to indicate the different conformational states accessible to the protein during the simulations. The Molecular Mechanics / Poisson-Boltzmann Surface Area (MM/PBSA) method was used to identify key residues involved in IDE rearrangement.
Evaluation of AutoDock and AutoDock Vina on the CASF-2013 benchmark

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Computer-aided protein-ligand binding predictions are a valuable help in drug discovery. Protein-ligand docking programs generally consist of two main components: a scoring function and a search algorithm. It is of interest to evaluate the intrinsic performance of scoring functions, independently of conformational exploration, to understand their strengths and weaknesses, and suggest improvements. The comparative assessment of scoring functions (CASF) provides such an evaluation. Here we add the AutoDock and Vina scoring functions to the CASF-2013 benchmark. We find that these popular, free software docking programs are generally in the first half (AutoDock) and first quarter (Vina) among all methods tested in CASF-2013. Vina is the best of all methods in terms of docking power. We also find that ligand minimization has an important impact, reducing the performance difference between AutoDock and Vina.
Molecular dynamics simulations of hydrophobic gating in the TMEM175 channel: the effect of polarisability and water model

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Ion channels are an important class of proteins that enable ions and water to pass through cell membranes. In some of these ion channels there is a ‘hydrophobic gate’ – a region within the channel cavity which is lined by hydrophobic residues and within which a ‘vapour lock’ is formed thereby closing the channel off to the passage of water and ions (1). The existence of a vapour lock is a function of the radius of the channel and the degree of hydrophobicity of the channel lining (2). Crucially, there is no steric occlusion of the pore. Molecular dynamics simulations are a powerful tool for probing this wetting/de-wetting behaviour, however the methods for modelling water are many and varied e.g. water molecules can be represented using rigid fixed-charge or polarisable models (3). Using the TMEM175 ion channel as a test case, we explore the effect of radius, hydrophobicity, polarisability and water model on molecular simulations of hydrophobic gating.

DNA packaging in bacteriophages: The effect of DNA – capsid interactions

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DNA packaging and ejection are two critical moments in dsDNA bacteriophages lifecycle. The understanding of these two processes is decisive for the effective application of phages as an alternative to antibiotics or in gene therapy. Several factors determine the conformation of the confined DNA, which include the forces needed to pack the DNA molecule to near crystalline density, the geometrical constrains and the chemical structure of the phage major capsid protein. In particular, features such as DNA orientation, the layered structure near to the wall and especially the detailed structure of the outer layer are strongly linked to the correlation between the DNA and the inner wall of the phage proteinaceous capsid, rather than the polymeric structure of the DNA itself. In previous communications we have shown how the final conformation of the packaged DNA molecule, predicted by Molecular Dynamics simulations, shows features that agree with cryoEM and X-ray diffraction experiments. These simulations mimicking the packaging process in phage φ29 used oxDNA model for the dsDNA molecule and a homogenous repulsive wall for the capsid. However, the atomic roughness and charge distribution of the inner surface of the capsid shown by cryoEM experiments may be important for the existence of DNA patterns next to the capsid wall of certain viruses. In an effort to include the detailed atomic structure of the capsid in our simulations, we have developed a coarse-grained model coupling an atomistic approach for the capsid with the oxDNA coarse grained model for the dsDNA molecule.

* Speaker
Investigating Ion-Exchange Adsorption of Proteins through Experiments and Molecular Dynamics Simulations

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Chromatographic processes, especially Ion Exchange Chromatography (IEC), are extensively used in protein purification. However, their industrial scale-up remains under-optimized and is still based on empirical methods. Today, their cost represents up to 80-90% of the global cost for protein production. The protein adsorption on chromatographic media has been thoroughly investigated over the past decades, in terms of surface properties, influence of pH and/or ionic strength as well as protein characterization in single and multicomponent systems. The aim of this work is to better understand the protein binding mechanisms on adsorbents using Molecular Dynamics (MD) simulations. Indeed, MD simulations are a powerful tool and allow the study at the atomic level without requiring microscopic experimental techniques. The steric mass action (SMA) model, which accounts for the steric hindrance of the protein, is widely used to describe single adsorption isotherms and depends on different parameters such as the characteristic charge of the protein, the steric factor and the equilibrium constant. These parameters were obtained both experimentally and through MD simulations for a protein (α-chymotrypsin) and a well-known resin (SP Sepharose FF) chosen as models. It allows validating the relevance of microscopic simulations to predict the protein adsorption behavior in adsorbents and then avoid long and costly experiences. This, in turn, enables simulation-based improvement of protein purification process which may have strong industrial impact.

*Speaker
Antibodies are a fast-growing class of biotherapeutic proteins, opening novel treatment avenues to tackle various diseases. They adopt a Y-shaped structure, which consists of four polypeptides, two heavy and two light chains, which can be further subdivided into different domains. For modeling and engineering such antibodies, the relative interface orientation between two immunoglobulin domains plays a central role, as they co-determine various biophysical properties. For example, the interface between the two variable domains (VH-VL) has been linked to conformational changes in the binding site geometry, directly influencing the antigen binding process. Other interfaces, such as the CH3-CH3 and CH2-CH2 interfaces found in the antibodies Fc region are of similar interest, as they are involved in the interaction of the antibody with various receptors of the immune system. While previous approaches to characterize the orientation of the VH-VL interface exist, no such approach was extended to the Fc region interfaces. We therefore present the ‘Orientation of Cylindrical Domains (OCD)’ tool, implementing a transferable approach to calculate inter-domain orientations for all immunoglobulin domains. Based on a user-supplied reference structure, the tool automatically builds a reference coordinate system based on physical characteristics of the reference. Through alignment, this coordinate system can then be mapped onto a sample structure to calculate six measures which fully characterize the inter-domain orientation. The tool can handle static structures as well as MD simulation trajectories and is therefore especially suited to investigate the dynamic characteristics of such domain interfaces. The Python-based OCD tool is available at https://github.com/liedllab/OCD.

*Speaker
Antibodies are very important proteins of the immune system. These proteins are Y-shaped and can be split up into two antigen-binding fragments (Fab) and one crystallizable fragment (Fc). A Fab consists of a heavy and light chain and can be subdivided into a variable (VH and VL) and a constant region (CH1 and CL). The variable region contains the complementarity-determining region (CDR), which is formed by six hypervariable loops, shaping the antigen binding site, the paratope. Apart from the CDR loops, both the elbow angle and the relative interdomain orientations of the VH–VL and the CH1–CL domains influence the shape of the paratope. Thus, characterization of the interface and elbow angle dynamics is essential to antigen specificity. We studied nine antigen-binding fragments (Fab) to investigate the influence of affinity maturation, antibody humanization, and different light-chain types on the interface and elbow angle dynamics. While the CDR loops reveal conformational transitions in the micro-to-millisecond timescale, both the interface and elbow angle dynamics occur on the low nanosecond timescale. Upon affinity maturation, we observe a substantial rigidification of the VH and VL interdomain and elbow-angle flexibility, reflected in a narrower and more distinct distribution. Antibody humanization describes the process of grafting non-human CDR loops onto a representative human framework. As the antibody framework changes upon humanization, we investigated if both the interface and the elbow angle distributions are changed or shifted. The results clearly showed a substantial shift in the relative VH–VL distributions upon antibody humanization, indicating that different frameworks favor distinct interface orientations. Additionally, the interface and elbow angle dynamics of five antibody fragments with different light-chain types are included, because of their strong differences in elbow angles. For these five examples, we clearly see a high variability and flexibility in both interface and elbow angle dynamics, highlighting the fact that Fab interface orientations and elbow angles interconvert between each other in the low nanosecond timescale. Understanding how the relative interdomain orientations and the elbow angle influence antigen specificity, affinity, and stability has broad implications in the field of antibody modeling and engineering.
Uncover the experimental 3D structure of transmembrane proteins is a complicated task in structural biology. As of May 2021, the number of experimentally solved structures for G-protein coupled receptors (GPCRs) is limited to circa 95 out of 800 family members. The structure of the human melanocortin receptor 4 (MC4R), a GPCR involved in the regulation of hunger and satiety mechanisms and a primary target for anti-obesity drugs, was recently solved by Cryo-EM. The structure was solved in complex with the agonist setmelanotide, a cyclic peptide recently approved for the treatment of obesity, and with the Gs heterotrimer, and revealed the mechanism of satiety*. Molecular dynamics simulations (MDs) of the MC4R/setmelanotide complex computationally validated the presence of a Ca2+ binding site located in the proximity of the MC4R orthosteric binding site. Together with mutagenesis experiments conducted on the residues involved in Ca2+ binding, the computational data shed light on the protein/ligand Ca2+ coordination and on the reduced receptor activation level observed in absence of this divalent ion. In addition, a comparison with the available inactive structure reveals the mechanism for MC4R activation, highlighting a molecular switch that triggers the satiation signal. These results fill a gap in understanding MC4R activation and could guide the design of new potent drugs essential for obesity treatment. * Israeli H. et al. Structure reveals the activation mechanism of the MC4 receptor to initiate satiation signaling. Science (2021).
The simulation of amyloid-beta (Aβ) aggregation considering in vivo conditions

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The misfolding of the amyloid-β peptide (Aβ) and its subsequent formation into toxic oligomers is membrane-driven, and this process is central to the prevailing hypothesis on Alzheimer’s disease progression. We use atomistic molecular dynamics (MD) simulations to simulate the aggregation of Aβ in environments that consider certain conditions within the brain, such as oxidative stress, the neuronal membrane composition and the crowding effect. In this regard, we utilized Hamiltonian replica exchange MD simulations to elucidate the impact of selected oxidized glycine residues of Aβ42 on the interactions of the peptide with a model membrane comprised of 70% POPC, 25% cholesterol, and 5% of the ganglioside GM1. The main findings are that, independent of the oxidation state, Aβ prefers binding to GM1 over POPC, which is further enhanced by the oxidation of Gly29 and Gly33 and reduced the formation of β-sheet. We further use atomistic MD simulations and transition networks to stepwise elucidate the oligomerization process, starting from the dimerization of Aβ42 in the aqueous phase and in the presence of a lipid bilayer (with six lipid component) mimicking the in vivo composition of neuronal membranes. The dimerization in solution is characterized by a random coil to β-sheet transition that seems on-pathway to amyloid aggregation, while the interactions with the neuronal membrane decrease the order of the Aβ42 dimer by attenuating its propensity to form β-sheet structure. The main lipid interaction partners of Aβ42 are the surface-exposed sugar groups of GM1. As the neurotoxic activity of amyloid oligomers increases with oligomer order, these results suggest that GM1 is neuroprotective against Aβ-mediated toxicity. Finally, we simulate the dimer and hexamer formation of Aβ16-22 fragment in the aqueous phase in crowded (30% crowder being present and modeled as neutral sphere) and non-crowded environment. The main finding, is that crowder stabilizes the aggregation.

*Speaker
Towards better understanding of sweet-tasting molecules

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Sweet taste is mediated via the Family C GPCRs dimer T1R2/T1R3. Most known sugars and sweeteners bind to the Venus Fly Trap extracellular domain of the T1R2 subunit. A possible approach for finding new sweet molecules is through structure-based virtual screening by docking to sugar-binding site. Since no experimental structure of human sweet taste receptors is available yet, we evaluated several homology models and docking protocols by their ability to differentiate between true positives and decoys. Outward facing orientation of residues R383 was found to be more likely. The best performing models were then used for prospective virtual screening, uncovering newly patented sweeteners (1). Next, the model was used for rationalizing structure-activity relationship of compounds derived from licorice, and to discriminate sweet from non-sweet licorice compounds. Non-sweet licorice-tasting compounds did not surpass the docking score of the known sweet compounds. Analysis of docked sweet saponins indicated that it is important to form hydrogen bonds with residues N44 or Y103 (2). The saccharide moiety and the functional group at position C-30 were common among the sweet licorice compounds. The C-30 functional group formed hydrogen bonds with N44. These interactions appear important for the orientation of compounds to the upper lobe of the binding site typical for the sweet compounds, while non-sweet compounds, had lower docking scores, and were oriented towards the lower lobe of the binding site. Finally, though typically a change in chirality strongly affects ligand–receptor interactions, we show that L- and D-glucose across a few concentrations are perceived as similarly sweet by humans, and that in cell-based functional assays, both enantiomers activate the human sweet taste receptor TAS1R2/TAS1R3 (3). Docking suggested that glucose enantiomers can bind in either one of two subpockets of the VFT domain of TAS1R2, each overlapping with the predicted positions of monosaccharide units of sucrose. The compatability of each of the hydroxyl-rich enantiomer is enabled by multiple hydrogen-bond donors and acceptors in the binding subpockets.

∗Speaker
Deep learning protein conformational space with convolutions and latent interpolations

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Determining the different conformational states of a protein and the transition paths between them is key to fully understanding the relationship between biomolecular structure and function. This can be accomplished by sampling protein conformational space with molecular simulation methodologies. Despite advances in computing hardware and sampling techniques, simulations always yield a discretized representation of this space, with transition states undersampled proportionally to their associated energy barrier. We present a convolutional neural network that learns a continuous conformational space representation from example structures, and loss functions that ensure intermediates between examples are physically plausible. We show that this network, trained with simulations of distinct protein states, can correctly predict a biologically relevant transition path, without any example on the path provided. We also show we can transfer features learned from one protein to others, which results in superior performances, and requires a surprisingly small number of training examples.
Discovering three-dimensional biomolecular shapes for a small number of two-dimensional XFEL diffraction patterns

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Single particle X-ray Free Electron Laser (XFEL) scattering promises to probe biomolecular complexes without crystallization, near physiological conditions at room temperature. However, to be able to reconstruct a three-dimensional structure requires large numbers of good quality diffraction patterns and expensive computation to determine the orientation of the particle and phase information. To mitigate some of the current limitations and provide a tool for exploratory analysis, we propose a novel approach to discover plausible 3D biomolecular shapes from a limited number of single particle XFEL data. In our strategy, small sets of five input XFEL diffraction patterns, simulated to mimic experimental data, can be searched against a library of diffraction patterns created from a database of 1628 non-redundant single particle cryo-electron microscopy (EM) models to find potential 3D models. The EM models were to low-resolution gaussian mixture models, and normalized their volumes to reduce redundancy. Then the diffracted patterns were created from evenly sampled projections of these gaussian mixture models. For the matching protocol, we implemented a method that fits the radial intensity profiles to the spherical form factor function to find the best matching regions on the diffraction patterns for accurate alignment. The protocol retrieved the same EM model as a top ranking match for every test input set, despite having been created independently from the patterns in the library and having sparser intensities. While increasing the number of input diffraction patterns improved the quality of the rest of the matches in some cases, the results were more dependent on the uniqueness or complexity of the shape as captured in the individual input diffraction patterns, and the availability of a similar 3D biological shape in the search library. As single particle XFEL methods are still in their infancy, our tool provides an opportunity to interpret novel data quickly to guide further analysis. We plan to expand the library of diffraction patterns to include more known structures across different methods.

*Speaker
New Quinolines Derivatives for Antimalarial activity: Docking, ADMET and Drug-likeness Studies

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Malaria persists as the most infectious vector-borne disease in the world. The objective of this work is to perform a theoretical analysis of the antimalarial activity of a series of 4-oxoquinoline and 4-hydroxyquinoline derivatives A-D in order to rationalize the available experimental results and to design new potent derivatives E-F, using the molecular docking technique. The study of molecular geometries was carried out in gas phase at the DFT/B3LYP/6-31+G(d,p) computational level. Moreover, ADMET-related descriptors have been calculated to predict the pharmacokinetic properties (PK) of the studied compounds. As results, we found a good agreement between the theoretical and the experimental geometrical parameters. The visualization of the docking simulation show that the 4-oxoquinoline compounds are a potential antimalarial activity compared to 4-hydroxyquinoline derivatives and is in agreement with experimental results. It turns out that compounds E and F are predicted to be better antimalaria than the reference and other derivatives A-D.
Averting side effects and improving specificity and efficacy of novel \( \mu \)-opioid receptor (MOR) agonists guided by Site Identification by Ligand Competitive Saturation (SILCS)


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**Opioids are hailed as the "Holy grail" of medicine because of their exceptional antinociceptive abilities. However, such exceptional antinociceptive abilities of opioid alkaloids are accompanied by addictive properties, euphoria, respiratory depression, and constipation, to name just a few. Overcoming such adverse effects, while retaining the potency and efficacy, has remained a challenging aspect of the design of efficacious opioids. Of the wide range of opioids, the 4,5-epoxymorphinan moiety has been established as the key "address" site of opioids that carries the "message" to all isoforms of the opioid receptors - \( \mu \), \( \delta \) and \( \kappa \). Substitutions on the 4,5-epoxymorphinan ring delivers the "message-address" concept differently to these isoforms, despite the known similarities in their active binding pockets. In the present study, we identify the chemical interactions of these substitutions with the receptor pockets, elucidating the Structural Activity Relationship (SAR) of a collection of 4,5-epoxymorphinan based novel ligands, guided by the Site Identification by Ligand Competitive Saturation (SILCS) approach. SILCS is a computational drug design approach that utilizes all-atom Molecular Dynamics (MD) simulations hybrid with a Grand Canonical Monte Carlo solute sampling scheme. The binding affinity pattern of the solutes is then stored in the form of fragment maps (FragMaps), which are used to identify novel binding sites and in SILCS based Monte-Carlo docking, where ligands are docked on these FragMaps to identify their binding orientations and affinity though a free energy score called LGFE (Ligand Grid Free Energy). Applying this approach to \( \mu \)-opioid receptor we identified the contribution of different substituents on a series of 4,5-epoxymorphinan compounds thereby facilitating interpretation of the experimental binding affinities. The SAR information along with the experimental binding affinities shall be used for the future design of novel, more specific opioids with reduced adverse effects common to traditional opioid alkaloids.**

*Speaker
Irreversible Cu(I) Transfer From Atx1 to Ccc2 Protein: A Theoretical Study

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Copper chaperone delivers copper ions to specific physiological partners by direct protein–protein interactions. In this study, a detailed mechanism for the copper transfer between the yeast Atx1 and Ccc2a (P-type-ATPase) is proposed. To explore the potential energy surface (PES) of the reaction pathway, Density Functional Theory (DFT) based B3LYP/6-31+G**Lanl2DZ method was used for the active site model. The effect of protein environment on the reaction pathway was unravelled by Our own N-layered Integrated molecular Orbital and molecular Mechanics (ONIOM model) using B3LYP/6-31+G**Lanl2DZ:UFF method is shown in Figure 1. Results obtained from the calculations unveil the formation of kinetically stable 3-coordinated intermediate IM3(ONIOM). It also provides information on the irreversibility of Cu(I) transfer from Atx1 to Ccc2a domain. The proposed mechanism enables us to understand the rate determining step and activation barrier of the transfer, which is 14.15 kcal/mol for active site model and 22.87 kcal/mol for ONIOM model. It is evident from NBO analysis that the interaction between K65-Atx1 and Cu(I)–S3 unit is mediated by the water molecule which is responsible for the stabilization of 3-coordinate intermediate. These results provide a new insight into the Cu(I) transfer mechanism in chaperones.
Design of a Novel Multi Epitope-Based Vaccine for Pandemic Coronavirus Disease (COVID-19) by Vaccinomics and Probable Prevention Strategy against Avenging Zoonosis

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The emergence and rapid expansion of the coronavirus disease (COVID-19) require the development of effective countermeasures especially a vaccine to provide active acquired immunity against the virus. This study presented a comprehensive vaccinomics approach applied on the complete protein data published so far in the NCBI coronavirus data hub. We identified non-structural protein 8 (Nsp8), 3C-like proteinase, and spike glycoprotein as potential targets for immune responses to COVID-19. Epitopes prediction illustrated both B cell and T cell epitopes associated with the mentioned proteins. The shared B and T cell epitopes: DRDAAMQRK and QARSEDKRA of Nsp8, EDMLPNYEDL and EFTPFDVVR of 3C-like proteinase and VNNSYECDIPI of the spike glycoprotein are regions of high potential interest and have high likelihood of being recognized by the human immune system. Vaccine construct of the epitopes shows stimulation of robust primary immune responses and high level of interferon gamma. Also, the construct has the best conformation with respect to the tested innate immune receptors involving vigorous molecular mechanics and solvation energy. Designing of vaccination strategies that target immune response focusing on these conserved epitopes could generate immunity that not only provide cross protection across Betacoronaviruses but additionally resistant to virus evolution. Results from simulations depicted a time dependent dynamics of peptide while a preventive strategy is also discussed in this work creating a need to protect the extinction of various species caused by Homo sapiens. The whole workflow is shown in Figure 1 while binding conformation of MEPVC with TLR3 and TLR4 are depicted in Figure 2 and Figure 3, respectively. Connection of antibiotic resistance along with antibiotic’s overuse especially under COVID pandemic, and results of a combination therapy in one of our research work will be discussed at the end of oral presentation.
Inhibiting RNA:Protein Interactions using an Integrative Computational and Experimental Approach: Application to Y Box Binding Protein 1

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While targeting Protein:Protein interactions has served as basis for the development of new drugs, RNA:Protein interactions, which are as important in human pathologies, notably cancer, is very promising but remains largely unexploited. One of the major mRNA binding proteins is YB-1, a master regulator of translation in cancer cells. It has been recently considered as a therapeutic target for the treatment of cancer and drug-resistant cancer. However, no small molecules with high affinity and specificity against YB-1 have been proposed so far along with the structural data essential to interrogate their relevance.

The conception of drug candidates is a very delicate procedure that requires a prior understanding of the translation regulation systems at the atomistic level using a high level of accuracy and state-of-the-art techniques. And connecting in silico data to structural data from diverse experimental resources is mandatory to provide a resolved picture of the underlying mechanisms. Hence, combining both advanced computational and experimental techniques will help integrate chemical, structural and cellular data for the development of small molecules that target RNA:YB-1 interactions. This is done by developing an innovative approach that would integrate a) molecular modeling data (Drug design, Molecular Dynamics and Free Energy Simulations using a sufficiently accurate computational model that is computationally efficient), b) NMR Spectroscopy data, c) together with an experimental validation in cells with a new HCS technology, "MT Bench", that quantifies RNA:protein interactions at the single cell level. The major advantage is providing cellular and structural data to feed, with little delay, the computational approach to propose efficient and specific ligands that target translation regulation in vitro and in cancer cells.

This approach allowed us, for now, to identify several promising active compounds in the sub-micromolar range. We will focus, in a next step, on rationally optimizing them to help propose new anti-cancer drugs able to overcome drug resistance by targeting YB-1 with a higher affinity and a larger selectivity.

*Speaker
Determination of Vibrational Circular Dichroism spectra of biomolecules through a classical dynamic approach using polarisable force fields

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Vibrational circular dichroism (VCD) is the weak difference in absorption for chiral molecules between right- and left- polarized light in the infrared range. It has promising applications in pharmacology owing to its ability to determine absolute configurations of chiral molecules. The shape of VCD spectra is highly sensitive to minor changes in conformation and molecular interactions, which makes it a sensitive probe of conformational isomerism and solvation.(1) Most approaches in VCD studies so far have rested on static (2) and dynamic DFT calculations. (3, 4) These calculations are computationally demanding and associated with short exploration times. We propose a classical molecular dynamics approach using the AMOEBA polarisable force field (5) to extend the exploration time with an accurate description of the electrostatic interactions. This method has been recently implemented in the Tinker software package (6) and takes into account anharmonic and temperature effects. Initial work has been done to include the chemical environment of the biomolecule explicitly. Here we will present the first results obtained with this new implementation on amino-acids.

References:

*Speaker
Divalent Cations and Ribozyme Catalysis: a Molecular Dynamics Study

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RNA enzymes, called ribozymes, are found to be involved in an increasing number of biological processes. Understanding the origin of their catalytic activity is a major biochemical challenge to be able to control, to modify, or to tune their activity. An intriguing question pertains to the role played by divalent cations in the ribozyme activity: in vivo, their activity is often associated with the presence of Mg2+ ions. However, the cation-specificity of ribozyme activity strikingly differs between closely related sequences and depends on distant tertiary contacts. However, despite a large number of experimental and computational studies, the molecular origin of divalent ions specificity in ribozyme catalysis is still not fully understood.

In this work, we aim to unveil the role of divalent cations in the activity of the model Hammerhead ribozyme at the molecular level. This first requires to characterize the impact of cations on the ribozyme active site conformation. From a computational/simulation perspective, this aspect is especially challenging because of the high structural flexibility of ribozymes, much larger than that of protein-based enzymes, which requires appropriate, and computationally-expensive, sampling strategies. Besides, the interaction between RNA and divalent cations is notoriously difficult to describe due to polarization and charge transfer effects. We will present our results that highlight how the choice of the level of description (force field) and of the sampling strategy have a critical impact RNA conformational dynamics and RNA–cation interactions.

*Speaker
Missense mutations modify the α-helix and β-sheet content of the conformational ensemble of α-synuclein monomer which exhibits a two-phase characteristic

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α-synuclein is an intrinsically disordered protein (IDP) occurring in different conformations and prone to aggregate in β-sheets structures, which are the hallmark of the Parkinson disease. Missense mutations, A30P, E46K and A53P are associated to familial forms of PD. How these single amino-acid substitutions modify the conformational ensemble of WT α-synuclein is unclear. Here, using coarse-grained molecular dynamics (MD) simulations, we sampled the conformational space of WT and mutant α-synuclein monomers for a total effective time scale of 14.5 ms (72 replicas of 200 µs each). To characterize the α-synuclein structures, we developed an algorithm, CUTABI (CUrvature and Torsion based of A-helix and B-sheet Identification), to identify residues in α-helix and β-sheets from Cα coordinates. CUTABI was built from the results of all-atom DSSP algorithm by analyzing 14,652 selected protein structures (2.3 million residues) of the protein data bank. DSSP results are reproduced with 93 per cent of success for a computational cost about 30 times less as all-atom reconstruction of the coarse-grained structures is avoided. Effective free-energy landscape (FEL) of α-synuclein as function of the number of residues in α-helices and in β-sheets is computed for WT and mutants from the analysis of the structures generated by Replica-Exchange MD. For WT and mutants, the Density Of conformational States (DOS) reveals a two-phase characteristic with a homogeneous phase (only β-sheet, global minimum of the FEL) and a heterogeneous phase (mixture of α-helix and β-sheet, local minima of the FEL). The majority of structures are within 2kT (at 310K) of the global minimum corresponding to a majority of about 50 residues in β-sheets. A53T and A30P DOS differs from the WT. In addition, A53T has a significant larger propensity to form helix than the others. These findings indicate that the equilibrium between the different conformational states of α-synuclein monomer is modified by the missense mutations in a subtle way. The α-helix and β-sheet contents are promising order parameters for IDP as other structural properties as gyration radii cannot discriminate significantly the WT and mutant conformational ensembles.

*Speaker
Parameterization Made Easy With ParaMol

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Thorough and accurate simulation of molecular configurational ensembles is crucial to predict theoretical static properties such as optical spectra, NMR spectra, and free energies. Owing to the computational feasibility of molecular mechanics (MM) methods, these are widely used in chemical sciences, often allowing simulation of long timescales that permit ergodic sampling to be achieved or, at least, approached. In this context, force fields (FF) are commonly employed to describe the potential energy function of systems of interest and to simulate their dynamical behaviour. Despite FFs’ low computational cost, their accuracy is frequently hindered by functional form constraints and poor transferability of parameterization. Among the several functional forms proposed thus far, the class I additive potential energy function is employed in the majority of atomistic biomolecular simulations, for which accurate FF parameters for biomolecules like proteins or DNA are available. Nevertheless, reliable parameters are usually unavailable for novel molecules such as drug candidates, as these may involve functional groups and interactions that are particularly challenging and system-specific.

In this work, we present the ParaMol (1), software that has a special focus on the parameterization of bonded and nonbonded terms of class I FFs by fitting to ab initio data. We describe the theory underlying ParaMol’s parameterization philosophy, as well as its several features, viz. the capability of performing self-consistent parameterization, dihedral scans, RESP fitting, among other available tasks. Additionally, we illustrate the software’s capabilities with application examples and report the best practices to be applied alongside each parameterization recipe. Owing to ParaMol’s capabilities and high efficiency, we propose that this software can be introduced as a routine step in the protocol normally employed to parameterize druglike molecules for MM simulations.


*Speaker
Effect of Resonance Width in the Investigation of Dissociative Electron Attachment Cross – Section to Some Bio Molecules

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Dissociate electron attachment (DEA) is of the phenomena of electron-molecule scattering event. In DEA, when an extra electron attaches to a target molecule it forms a metastable species which further fragments to different products. We have been involved in delineating DEA cross-section to some bio-fragments through computationally modelling studies (1-7). Our investigation involved both electronic structure theory and quantum molecular dynamics approaches. We have seen that resonance width which controls the lifetime of the metastable anion has a tremendous effect on the DEA cross-section [8]. A detailed study on the effect on resonance width in DEA cross-section will be presented in my talk.

References
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(8) M. Sarma (In preparation)

*Speaker
Capturing Water Networks During Ligand Binding with the Site-Identification by Ligand Competitive Saturation Approach

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Water molecules impact interactions between proteins and their ligands, making a significant contribution to ligand binding orientation and affinity. Water molecules can significantly affect the energetics of ligand binding in a favorable or unfavorable manner associated, in part, with the energetic penalty for displacing waters that occupy a binding site. In computer-aided drug design, the challenge is to calculate water mediated interactions and their energetics between the ligand and the protein. In this work, an extension of the Site Identification by Ligand Competitive Saturation-Monte Carlo (SILCS-MC) docking approach is presented to determine the positioning of the water molecules in the binding site and estimate the energetic contribution of water to ligand binding. We employ this methodology on variety of protein targets where water mediated interactions between the protein and ligands plays an important role. The efficacy of this approach is reflected in rank-ordering ligand affinities, binding affinities predictions, and structure orientation of the ligands. The SILCS methodology is of utility for characterization of functional group affinities for the entire 3D region encompassed by a protein or other macromolecule. This approach is based on sampling the conformational space of multiple solutes representing various functional groups in the presence of explicit water of a protein target using a combination of oscillating chemical potential Grand Canonical Monte Carlo and Molecular Dynamics simulations. The presented approach offers new possibilities in revealing water networks and their contributions to the binding affinity of a ligand to a protein.

*Speaker
Inhibitors of human neutrophil elastase against proteinase 3: A multisite lambda dynamics (MSLD) study

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Chronic obstructive pulmonary disease (COPD) is a progressive lung disease that comprises emphysema, asthma, and bronchiectasis. The WHO lists COPD as the third leading cause of death worldwide. Neutrophil serine proteases (NSPs) are known to be involved in the pathophysiology of COPD. They are responsible for the degradation of extracellular matrix proteins and are also involved in the resolution of inflammation. Neutrophil elastase (HNE), a key NSP has been a drug target for more than two decades and another NSP, proteinase 3 (PR3), is a new emerging potential target. There are several Small MOLecule (SMOL) inhibitors of HNE in the literature but, the most interesting ones are the 4th and 5th generation noncovalent inhibitors from Bayer HealthCare AG. While several X-ray structures of HNE bound to SMOL are available in the Protein Data Bank, there is only one structure of PR3 in its apo form. Only a few SMOL inhibitors have been reported for PR3. The availability of affinity data for the 4th and 5th generation Bayer compounds for HNE provides an opportunity to evaluate MSLD and the ability of the CGenFF force field to reproduce relative binding affinities for these compounds. Eventually, it also allows us to map the structure-activity relationships of these compounds on PR3. Ten Bayer compounds with an IC50 range from 0.03 to 69 nM were chosen for relative free energy calculations with HNE. The 3D structures of the compounds were generated by MarvinSketch and superimposed on the ligand in PDB ID 5A8X. MSLD was used with CHARMM36 and CGenFF (or Antechamber/CGenFF) force fields to calculate relative binding free energies. The Antechamber/CGenFF modification contained AM1-BCC charges. MSLD sampled 9 out of 10 substituents irrespective of the force field used. The Pearson correlation between experimental IC50s and ΔΔG from MSLD with CGenFF was 0.2 which improved to 0.6 with modified charges. Although MSLD was very efficient there is still room for improvement in high penalty parameters from CGenFF such as torsions (soft degrees of freedom). All these optimizations from the original CGenFF will finally help us to map the SAR of present and future compounds on PR3.

*Speaker
Quantum and classical effects in DNA point mutations: Watson-Crick tautomerism in AT and GC base pairs

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Proton transfer along the hydrogen bonds of DNA can lead to the creation of short-lived but biologically relevant point mutations (1, 2) that can lead to gene mutation and, potentially, cancer. In this work, the energy landscape of the canonical A-T and G-C base pairs (standard, amino-keto) to tautomeric A*-T* and G*-C* (non-standard, imino-enol) Watson-Crick DNA base pairs is modelled with density functional theory and machine-learning nudge-elastic band methods. We calculate the energy barriers and tunnelling rates of hydrogen transfer between and within each base monomer (A, T, G and C). Using a purely quantum mechanical approach, we show that the role of tunnelling in A-T tautomerisation is statistically unlikely due to the presence of a small reverse reaction barrier. On the contrary, the thermal populations of the G*-C* point mutation could be non-trivial and propagate through the replisome. For the direct intramolecular transfer, the reaction is hindered by a substantial energy barrier. However, our calculations indicate that tautomeric bases in their monomeric form have remarkably long lifetimes. On the other hand, the quantum motion of the protons could be treated separately within an open quantum systems approach (3), where the system is evolved while coupled to a thermal bath of quantum oscillators representing its surrounding cellular environment of water molecules (4). This combined modelling of the potential energy surface and open quantum systems can accurately account for proton tunnelling in a biological environment, which could play a relevant role in DNA replication (5).


*Speaker
DNA is the molecule that nature uses as genetic material and it rarely exists in a relaxed state inside living beings. Rather, it is subjected to torsional, bending or stretching stress generated in cellular processes such as recombination, gene expression, replication, and more generally protein recognition. These tensions cause severe distortions on the double helix, which, in turn, influences its dynamic and recognition properties. I will show results about how DNA structure is affected by these different agents, including: (i) DNA supercoiling (1); (ii) the bacterial DNA-bending protein IHF (2); and (iii) the viral DNA unwinding protein helicase E1. I will also show how the different tools developed in the lab for analyzing the simulations help in the comparison of all-atom simulations with lower-resolution microscopy data (1,3).

Enhanced Sampling Molecular Dynamics, Maximum Entropy Reweighing, and HDX-MS Guided Ensemble Modeling: an approach to characterize the structure and dynamics of the cytoplasmic heme binding protein PhuS.

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Hydrogen-deuterium exchange coupled with mass spectrometry (HDX-MS) has established itself as a valuable biophysical approach which allows one to probe protein structure and dynamics. However, HDX-MS is limited to peptide level resolution. To that end, recent efforts have aimed to integrate HDX-MS with computational approaches to provide atomistic interpretation of the structural dynamics information garnered. In one such integrative approach, a HDX-MS based maximum entropy reweighting approach (HDXer) was employed to reweight computationally generated ensembles using HDX-MS data. In combination with dimensional reduction, HDXer can propose atomistic resolution ensembles representative of the HDX-MS data. Here, HDX-MS is used together with enhanced sampling MD simulations, HDXer, and dimensional reduction to characterize the structural dynamics of PhuS, a cytoplasmic heme binding protein from P. aeruginosa. PhuS is responsible for shuttling exogenous heme to Heme Oxygenase (HemO) for degradation and release of iron. This mechanism is critical in P. aeruginosa to sequester iron in iron sparse conditions and has further been shown to be critical in its growth and virulence. Although the crystal structures of unliganded (apo) and heme bound (holo) PhuS are nearly identical, HDX-MS of apo- vs holo-PhuS revealed large differences in deuterium uptake, notably in C-terminal proximal alpha helices 6, 7 and 8 (a6/7/8). These helices form part of the heme binding pocket and were observed to be mostly labile in apo-PhuS but were largely protected in holo-PhuS. In contrast, the predicted deuterium uptake of a6/7/8 in apo- and holo-PhuS obtained from MD simulations are highly similar to one another and in agreement with the HDX-MS data obtained for holo-PhuS, suggesting that the solution structure of apo-PhuS locally deviates from its crystal structure conformation. The combined use of enhanced sampling MD, HDXer and dimensional reduction reveals an apo-PhuS ensemble in which a6/7/8 are significantly rearranged compared to the crystal structure. The change in secondary structure was confirmed by circular dichroism spectroscopy of apo- and holo-PhuS. The resulting ensembles are then used for computational aided drug design (CADD) to develop candidate lead compounds.
Additive CHARMM36 Force Field for Nonstandard Amino Acids

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Nonstandard amino acids are both abundant in nature, where they play a key role in various cellular processes, and can be synthesized in laboratories, for example, for the manufacture of a range of pharmaceutical agents. In this work we have extended the additive all-atom CHARMM36 and CHARMM General force field (CGenFF) to a large set of 333 nonstandard amino acids. These include both amino acids with nonstandard sidechains, such as post translationally modified and artificial amino acids as well as amino acids with modified backbone groups, such as chromophores composed of several amino acids. Model compounds representative of the nonstandard amino acids were parametrized for protonation states that are likely at physiological pH of 7 and, for some more common residues, in both D- and L-stereoisomers. Considering all protonation, tautomeric, and stereoisomeric forms, a total of 406 nonstandard amino acids were parametrized. Emphasis was placed on the quality of both intra- and intermolecular parameters. Partial charges were derived using quantum mechanical (QM) data on model compound dipole moments, electrostatic potentials, and interactions with water. Optimization of all intramolecular parameters, including torsion angle parameters, was performed against information from QM adiabatic potential energy surface (PES) scans. Special emphasis was put on the quality of terms corresponding to PES around rotatable dihedral angles. Validation of the force field was based on molecular dynamics simulations of 20 protein complexes containing different nonstandard amino acids. Overall, the presented parameters will allow for computational studies of a wide range of proteins containing nonstandard amino acids, including natural and artificial residues.

∗Speaker
SerraNA/SerraLINE: Programs for analysing structural and flexibility properties of nucleic acids from simulation data

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In nature, the DNA molecule is rarely relaxed and during important processes such as DNA transcription/replication, the molecule is highly deformed by proteins. To understand how these biological processes work, we need to extensively understand the structural and elastic properties of DNA.

To study these properties, we have developed two programs for the analysis of molecular dynamics simulations of nucleic acids at the base-pair level, SerraNA and SerrLINE. These programs provide global parameters that are suitable for comparison with results from single molecule experiments.

*Speaker
Flexibility of homotetrameric pteridine reductase 1 enzyme from trypanosomatid human parasites in the complex with ligands, studied by molecular dynamics techniques.

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There is a need for improved treatments against trypanosomatid parasites causing devastating diseases of humans. Targeting the folate pathway of these parasites is one of the currently explored strategies to designing better anti-parasitic drugs. This requires inhibiting the trypanosomatid-specific protein - pteridine reductase 1 (PTR1). Experimental data show that PTR1 is inhibited by semi-products of the catalyzed reaction. PTR1 is a homotetrameric enzyme, thus the aforementioned substrate inhibition phenomenon may arise from long-distance coupling between its four subunits. Therefore, we aimed to computationally characterize dynamics and inter-subunit interactions of unbound and ligand-bound PTR1. First, normal mode analysis of the unbound enzyme shows the concerted movements of specific loops flanking PTR1 active sites. This is consistent with our preliminary analysis of the available crystallographic structures (1) and with the hypothesis of (anti-)cooperative dynamics of the PTR1 enzyme. Furthermore, our results show differing dynamics of the analyzed substrates and products bound to PTR1, which provides hints about substrate inhibition mechanism. The knowledge about the PTR1 enzyme dynamics will likely have implications for drug design against PTR1 and against other similar enzymes from the family of short-chain dehydrogenases/reductases, to which PTR1 belongs.

CHARMM General Force Field (CGenFF) Compass: A Lexical Dictionary Bridge from Functional Groups to their Atom Types.

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To understand a collection of atom types, organic and medicinal chemists adopted the IUPAC nomenclature to categorize functional groups. In this study a lexical dictionary bridge between IUPAC and CGenFF atom types is presented using SMILES/SMARTS common functional group patterns as the mid-level language translators. The CGenFF Compass highlights potential problematic compounds as well as identifies outlier patterns within a chemical dataset. Concomitantly, a keyword query language function was developed to obtain compounds based on the user’s interest in specific functional groups and rapidly identifying high scoring penalty atom types in those groups that may be targeted for parameter optimization. To visualize our classification schema, a sunbursting method was applied on one dimensional data over the course of four layers in this respective order: Functional Group, Relations of Functional Groups, Penalty Score, and Atom Type. The Penalty Score and Atom Type layers are based on high penalty scores determined from statistical analysis. Utilizing the sunburst method allowed us to illuminate a subsection of the Enamine database, compile a candidate list of unique patterns, and select 1,2-dithiolane to parameterize based on the sulphur and carbon ring atom types embedded in the cyclopentane ring. By using SMILES/SMARTS language keys to link different scientific data types, we constructed a Cheminformatic method to analyze and infer CGenFF performance.

*Speaker
Electronic-nose devices allow the detection of Volatile Organic Compounds (VOCs), and have a potential application in several fields, from rapid disease diagnostics to the detection of contaminated food, and air quality control. These devices comprise an array of sensors composed by different sensing materials. The usage of Odorant Binding Proteins (OBPs) as biosensors may increase VOC recognition and selectivity. OBPs are small soluble proteins found in vertebrates (lipocalin-like fold) and insects (globular α-helix), responsible for VOCs solubilization and transportation. OBPs have characteristic scaffolds and are able to recognize different compounds making them suitable for biosensor development.

An initial database comprising data from 22 OBPs (6 mammals and 16 insects) correlated with a total of 317 VOCs. The VOCs chemical properties were calculated, namely their chemical class, molecular weight, total surface area and polarity. Information from OBPs binding pockets was also extracted including the surface area, volume and polarity. The data from VOCs and OBPs was analysed to give an overview of the relationship between OBPs binding pockets and VOC affinity. A docking protocol to predict VOC-binding affinity automatically was proposed, but no direct correlation was found between the experimental $K_d$ values and the molecular docking function score prediction. Only for VOCs with higher molecular weight and larger surface area some correlation was observed.

Seven OBPs with unique and distinct characteristics in VOC molecular recognition in gas sensing were selected for experimental expression. Molecular dynamics simulations using GROMACS and amberff99-ILDN were performed in triplicates for each selected OBP. The simulations analysis of each OBP revealed that the binding pockets of these proteins tend to be more flexible in the insect scaffold than in the lipocalin-like scaffold of mammalian OBPs. These results validate the existing higher variability of ligand size for insect OBPs in comparison to mammalian ones.

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It was examined, whether the potential catalyze properties in relation to theoretical predictions of the acid – base properties of alkaline earth metal oxide could be enhanced, by combining them with alkaline metal oxide (1). The theoretical calculations were made using ab initio methods. The equilibrium structures and corresponding harmonic vibrational frequencies alkaline earth metal oxide \( \text{MO} \), dimers \( (\text{MO})_2 \) and mixed oxides \( \text{MON}_2\text{O} \), where \( \text{M} = \text{Be}, \text{Mg}, \text{Ca} \) and \( \text{N} = \text{Li}, \text{Na}, \text{K} \) were determined by applying the second – order Møller-Plesset (MP2) perturbational method with the aug-cc-pVTZ basis set. Then the electronic energies were refined using the coupled-cluster method with the single, double and non-iterative triple excitations (CCSD(T)) method in the same basis set. The basicity of the studied systems was determined by electronic proton affinity (PA), as a change in electron energy of the reaction: \( \text{B} + \text{H}^+ \rightarrow \text{BH}^+ \), where \( (\text{B} = \text{MO}, (\text{MO})_2, \text{MON}_2\text{O}) \) and gas-phase basicity, in turn the Lewis-acidity was determined by electronic hydride affinity (HA), as a change in electron energy of the reaction: \( \text{BH}^+ + \text{H}^- \rightarrow \text{BH}_2 \), where \( (\text{B} = [\text{MO}]\text{H}^+, [(\text{MO})_2]\text{H}^+, [\text{MON}_2\text{O}]\text{H}^+) \) and gas-phase electrophilicity. The basicities examined mixed oxides are increasing with rising atomic number \( \text{N} \), causing greater increase basicity in series of \( \text{MOL}_2\text{O}/\text{MON}_2\text{O}/\text{MOK}_2\text{O} \), than dimerization of alkaline earth metal oxide. In turn the Lewis-acidity of \( [\text{MOL}_2\text{O}]\text{H}^+/[\text{MON}_2\text{O}]\text{H}^+/[\text{MOK}_2\text{O}]\text{H}^+ \) systems decreases with increasing basicity of the corresponding mixed oxide. In all cases \( [\text{MO}]\text{H}_2, [(\text{MO})_2]\text{H}_2 \) and \( [\text{MON}_2\text{O}]\text{H}_2 \) systems are thermodynamically stable due to the fragmentation process of \( \text{H}_2\text{O} \) or \( \text{H}_2 \) detachment.

**References**


*Speaker
Specificity of *Loxosceles* α clade Phospholipase D enzymes for choline-containing lipids: role of a conserved aromatic cage

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Phospholipase D (PLD) enzymes are one of the major toxins in the recluse spider (*genus Loxosceles*) venom. *Loxosceles* PLD enzymes are classified in either the α clade or the β clade, and some correlation exists between α or β clade membership and high or low catalytic activity against sphingomyelin (SM), respectively. Lajoie et al., recently showed that a β clade enzyme from *Sicarius terrosus* (St_βIB1i) had a strong preference for substrates containing ethanolamine headgroups, and suggested that this substrate specificity originated from the interactions between the PLD interfacial face and lipids. To further understand the substrate specificity of these enzymes, we performed simulations of two PLDs from the α clade, *Loxosceles* intermedia αIA1 (Li_αIA1) and *Loxosceles* laeta αIII1 (Ll_αIII1), and one from the β clade, St_βIB1i. Simulations were performed in the presence of two types of lipid bilayers, choline-containing and ethanolamine-containing bilayer. We observed that the two α clade PLDs bound to bilayers with choline-containing lipids (PC or SM) using the catalytic loop. By contrast, St_βIB1i, did not bind to those bilayers. Analyses of the trajectories also reveal the importance, for the two α clade PLDs, of three aromatic residues located on the catalytic loop and forming a π-cage interacting with a choline group. A multiple sequence alignment of 18 PLDs of both clades reveals that the aromatic cage is conserved in a clade PLDs and absent from at least one major subgroup of the β clade enzymes. We suggest that this cage controls the affinity for choline headgroups, which is in agreement with earlier reports of PC lipid headgroups interacting with aromatic amino acids.

*Speaker
Exploring the effects of the F310S mutation on the structural dynamics of the PPARγ nuclear receptor

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Nuclear receptor proteins (NRs) are ligand-dependant transcription factors in animals that regulate gene expression controlling many physiological processes. Their canonical structure is composed of N-terminal domain, DNA binding domain (DBD), and ligand binding domain (LBD). Twelve α-helices make up the LBD, where helix 12 (H12) is responsible for interacting with co-regulator proteins after undergoing large-scale conformational changes. The Peroxisome Proliferator Activated receptor gamma, PPARγ, plays an important role in the regulation of lipid homeostasis, adipogenesis and insulin resistance. Recent collaborative research on the role of PPARγ in bladder cancer has identified gain- and loss-of function mutations in PPARγ.(1)

PPARγ with loss-of-function mutations has a larger affinity for co-repressor protein than the wild-type.(2) The structural consequences of loss-of-function mutations on co-repressor binding not known. This work focuses on the LBD mutation F310S. Due to the lack of detailed structural information for PPARγ complexed to co-repressor proteins, we modeled wild-type (WT) and mutant protein based on the structure of PPAR-α.

Molecular Dynamics simulations with MM/GBSA post-processing were used to obtain binding free energy estimates (ΔGbind) between the LBD and co-repressor peptide. This analysis showed better ΔGbind values for the mutant F310S than for the wild type (WT), consistent with experimental results. Visualization of structures extracted from the simulations showed a hydrophobic cluster around F310 residue in the WT, while in the mutant F310S structure, this cluster was structurally disturbed. We propose that this permits an increased flexibility of the H11-H12 loop and H12, so they can more freely rearrange around the co-repressor peptide to optimize the interactions. By further calculating solvation free energies, we identified 7 residues of H12 in the F310S mutant that showed more favorable interactions with co-repressor. The RMSFluctuations showed a decreased flexibility of H12 in F310S. We conclude that the lack of hydrophobic cluster in the mutant F310S could favour a conformational rearrangement of H12, leading to a higher number of interactions between receptor and co-repressor.

2. Coutos-Thévenot, L., Beji, S., et al, PPARγ is a tumor suppressor in basal bladder tumors offering new potential therapeutic opportunities, bioRxiv 868190; doi: https://doi.org/10.1101/868190

*Speaker
Rapid and accurate estimation of protein–ligand relative binding affinities using site-identification by ligand competitive saturation

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Predicting relative protein–ligand binding affinities is a central pillar of lead optimization efforts in structure-based drug design. The site identification by ligand competitive saturation (SILCS) methodology is based on functional group affinity patterns in the form of free energy maps that may be used to compute protein–ligand binding poses and affinities. Presented are results obtained from the SILCS methodology for a set of eight target proteins as reported originally in Wang et al. (J. Am. Chem. Soc., 2015, 137, 2695–2703) using free energy perturbation (FEP) methods in conjunction with enhanced sampling and cycle closure corrections. These eight targets have been subsequently studied by many other authors to compare the efficacy of their method while comparing with the outcomes of Wang et al. In this work, we present results for a total of 407 ligands on the eight targets and include specific analysis on the subset of 199 ligands considered previously. Using the SILCS methodology we can achieve an average accuracy of up to 77% and 74% when considering the eight targets with their 199 and 407 ligands, respectively, for rank-ordering ligand affinities as calculated by the percent correct metric. This accuracy increases to 82% and 80%, respectively, when the SILCS atomic free energy contributions are optimized using a Bayesian Markov-chain Monte Carlo approach. We also report other metrics including Pearson’s correlation coefficient, Pearlman’s predictive index, mean unsigned error, and root mean square error for both sets of ligands. The results obtained for the 199 ligands are compared with the outcomes of Wang et al. and other published works. Overall, the SILCS methodology yields similar or better-quality predictions without a priori need for known ligand orientations in terms of the different metrics when compared to current FEP approaches with significant computational savings while additionally offering quantitative estimates of individual atomic contributions to binding free energies. These results further validate the SILCS methodology as an accurate, computationally efficient tool to support lead optimization and drug discovery.

*Speaker
Rational design of modulators of skeletal myosin

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Skeletal myosin II plays a crucial role in muscle contraction and directed mechanochemical movement. The cyclic ATP-mediated interaction between actin and myosin in the sarcomere, known as the actomyosin cycle, mediates the shortening of the sarcomere, and on a macro-molecular scale, the contraction of striated muscle fibres. Altered interaction between actin and myosin can result in reduced myofiber force production which has recently been revealed to be an underling cause of potentially life-threatening muscular weakness, such as that experienced by nemaline myopathy patients. Treatment of nemaline myopathy, along with a range of other associated myopathies, currently relies on symptomatic relief only. Therapeutic intervention, which directly aims to modulate the actin-myosin interaction, may lead to possible treatment via compensation of the altered actin-myosin binding. In fact, the recent discovery of Omecamtiv Mercarbil, a cardiac myosin selective compound, and the first in class myotrope, has proved that direct targeting of sarcomeric proteins is possible, and promising. The aim of this project is to use a rational drug design approach to discover novel small molecules which can selectively bind skeletal myosin and activate it. Using homology modelling, we have been able to model the pre-power stroke and post-rigor structures of human skeletal myosin. Through virtual screening of compound libraries and molecular dynamics simulations, we have identified isoform-specific ligands with high predicted binding affinity. These will be further developed using structure-based drug design to increase selectivity and affinity to skeletal myosin. The most promising modulators will be validated by performing in vitro motility assays to confirm their mode of action.

*Speaker
Application of molecular dynamics to elucidation of the mechanism of glucose net and exchange transport via GLUT1

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Owing to the uncertainties of transport kinetics, the mechanism of net and exchange glucose transport via GLUT1 remains unclear, however extended atomistic molecular dynamics simulations of GLUT1 embedded in a fluid lipid membrane bilayer and surrounded by a physiological salt solution has resolved some of these ambiguities.

The first outstanding question is, does net glucose transport require conformational changes that alternately expose the central high affinity ligand binding site to externally and internally facing solutions, or does glucose transit by a random series of jumps between adjacent sites, aided by small fluctuations that randomly open and close the tunnels and cavities along the length of the central cleft?

By using a "flooding protocol" equivalent to 50 mM glucose in solution, molecular dynamics reveals a large number of amino-acids whose fluctuations alter with raised glucose concentration. These changes are most pronounced in the extra-membranous residues. With high solution glucose concentrations, the amplified fluctuations in GLUT1 allow glucose to permeate into the intramembranous regions. Glucose proximity to GLUT1 causes asynchronous expansions of bottlenecks occluding the internal and external openings of the central pore. This is accomplished by rotamer changes of large side chains of tyrosine, phenylalanine, and tryptophan residues, thereby permitting glucose and water to gain access to the central regions of the pore. Further, when glucose is close (< 6 Å) to five salt bridges formed between polar residues, e.g. lysine or arginine and glutamate or aspartate, located at the external and internal openings of the central pore, the distance between these residues tends to increase.

With this flooding protocol, several glucose traversals through the central region, considered as the high affinity docking site have been observed. Except for the flooding protocol, the transporter does not display any sign of spontaneous glucose penetration into the intramembranous regions.

*Speaker
Differential electrostatic properties of reaction model as a tool for prediction and reverse design of catalytic properties

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Electrostatic properties of transition state vs substrate models expressed as Differential Transition State Stabilization (1) field and potential maps have predictive power to assess the role of catalytic enzyme residues and even to predict dynamic changes in protonation states over the reaction course (2). Presented examples include prediction of proton dislocations enhancing ketosteroid isomerase catalytic activity and assessment of the role of the conservative residues of amino acid-tRNA synthetases. These observations open the way to reverse design of catalytic environment properties with limited computational cost (3).

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References

*Speaker
Towards the elucidation of a glucocorticoid and mineralocorticoid receptor ligand binding domain common dimerization interface

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The glucocorticoid (GR) and mineralocorticoid (MR) receptors both belong to the super-family of nuclear receptors (NRs) which are metazoan-specific and ligand-activated transcription factors that control the expression of target genes. GR and MR are close homologs and bind cortisol and aldosterone as natural ligands in human, respectively, i.e. small hydrophobic molecules. GR is involved in metabolism, development and inflammation while MR regulates electrolyte renal exchange and blood pressure. At the sequence level and from the N- to the C-terminus, GR and MR share a large N-terminal region, a highly conserved DNA binding domain (DBD), a short hinge region, a ligand binding domain (LBD) and a 10 residue C-terminal sequence or F-domain whose function has remained elusive. The LBD folds into a 12 α-helix sandwich that builds the ligand binding pocket. To activate the transcription of target genes, NR homo- or hetero-dimerize through an interface that involves LBD helices number 9, 10 and 11. However, the presence of the F-domain in GR and MR raises a steric obstacle to the formation of the homodimer. To understand how GR and MR may assemble, we searched all available X-ray crystals for protein-protein contacts. For each assembly, molecular dynamic simulations and binding free energy calculations were carried out to estimate the stability of the homodimers. In addition, the conservation of residues at the dimerization interfaces were determined. Popular programs such as ProtCID, PISA, PRISM, EPPIC and the molecular mechanics Poisson-Boltzmann surface area (MMPBSA) method were used to determine if any dimerization interface observed in crystals may show the features of a biological assembly. A consensus was reached by all methods and singled out an interface mediated by helices 9, 10 and the C-terminal F-domain whereas other interfaces were unlikely to be physiological. In patients, the prolonged administration of glucocorticoids is associated with severe side-effects such as osteoporosis, glycemia imbalance and muscle degeneration while acute renal deterioration is reported in dose-dependent MR antagonist therapies. Since these side-effects are thought to be the result of unregulated GR and MR target gene transcription, it is of major importance to understand how both receptors dimerize to mediate function.

*Speaker
Automation of Electrostatic Parameter Prediction to Extend Drude Force-Field to Novel Drug-Like Molecules

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CHARMM Drude force-field (FF) is well-established atomistic FF for biomolecules such as proteins, nucleic acids, lipids, and carbohydrates. Its ability to capture electronic polarization effects via auxiliary particle (Drude particles) attached to heavy atoms sets it apart from commonly applied additive FFs which rely on fixed charges. Extension of Drude FF to novel drug-like molecules is challenging as it requires an automated mechanism to assign atomic charges as well as polarizabilities to non-biomolecular systems. In the present work, we are developing a deep neural network (NN) model trained on quantum mechanical (QM) RESP charges, and atomic polarizabilities. A separate NN model has been developed for training Thole factors (term used to prevent catastrophic dipole-dipole interactions) against each atom-type. Current NN model is trained on around 42000 molecules obtained from ZINC-database with molecular weight up to 200 Dalton and containing H, C, N, O, S, P and halogen atoms. The chemical similarity of initial dataset is examined through Tanimoto similarity index and Morgan fingerprinting method. All the molecules were optimized at MP2/6-31+G(d) model chemistry, followed by RESP charge and atomic polarizabilities estimation at MP2/Sadlej model chemistry. A novel method has been developed to determine RESP charges on atoms as well as lone-pairs (external points), an integral feature of Drude FF. GDMA method was employed to calculate atomic polarizabilities which corresponds to Alpha term in Drude FF, while a MCSA fitting approach has been used to obtain the Thole term, which has no QM analog. The NN model utilizes bonded-connectivity of atom-types in Drude FF as features to build the model. To capture steric effects on the partial charges of lone pairs, distances between lone pair and nearby atoms is also used as features. The NN-based model is being validated by its application upon structurally larger drug molecules (FDA-approved). Such a NN-based electrostatic parameter predictor can prove to be very fast and chemically accurate in predicting molecular dipole and polarizabilities compared to reference MP2 calculations. We hope that the current NN model will harbing her the extension of Drude force-field to novel drug-like molecules.

*Speaker
A key question for the RNA world hypothesis is the emergence of autocatalytic networks in abiotic conditions that rely on ribozymes (RNA-enzymes) instead of protein-based enzymes. Currently, the ribozymes that are known to form self-replicating networks by catalyzing their own formation (ligation reaction) are too big to be formed from the short RNA fragments available in abiotic conditions. On the other hand, smaller ribozymes tend to favor their self-splicing, i.e., the backward reaction. A promising direction is to adapt specific environmental conditions (temperature, ions), strand sequence and length, which were shown by experiments to favor ligation e.g. in the small hairpin ribozyme, but an understanding of these factors’ impact on the catalytic steps is still missing. In this computational project, in collaboration with experimentalists, we combine state-of-the-art simulation methods to identify adequate sequences and conditions that favor ligation for small ribozymes and allow self-replication. In a first step, we first want to establish robust protocols to characterize the ribozyme structure both in the reactant and product states, using state-of-the-art enhanced sampling techniques. In particular, we show that the ribozyme active site is very flexible and its structure sensitively depends on the choice of force field, which will be shown to be critical for a reliable description of the conformational space exploration.
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