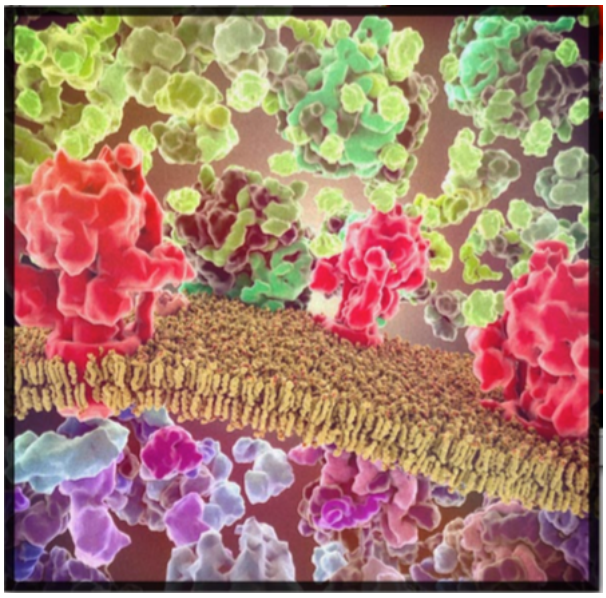
Centre Européen de Calcul Atomique et Moléculaire

Multiscale Modeling from Macromolecules to Cell: Opportunities and Challenges of Biomolecular Simulations



February 4, 2019 - February 6, 2019
CECAM – Lausanne (CH)

Giulia Palermo
University of California Riverside, USA

Valentina Tozzini
Istituto Nanoscienze - CNR, Italy

Matteo Dal Peraro
Swiss Federal Institute of Technology Lausanne (EPFL), Switzerland

Rommie Amaro
University of California San Diego, USA

Alexandre Bonvin
Utrecht University, The Netherlands

1 Description

Background and significance

Ever increasing advances in structural biology are challenging the field of multiscale modeling with the need of going beyond the limits of time scale and system-size of molecular simulations, modeling biological systems from the atomistic to the cellular level (CurrOpinStructBiol 2017, 43, 1). Thus, extending the simulations capabilities beyond the atomistic representation, invading the domains of bioengineering and bioinformatics, is of increasing importance for pursuing effective integrative research.

The aim of this workshop is to discuss these challenges, from atomistic to coarse grained (CG) and mesoscale (MS) representation of biomolecules into the cell environment, exploring novel integrative methods from the macromolecular (nm) to sub-cellular (μm) levels (AccChemRes 2017, 50, 594). These will include different kinds of phase space sampling, such as Brownian Dynamics (BD), advanced sampling methods and integrative methods that allow building structurally detailed 3D models of supra-molecular structures at cellular level.

Clearly, the limits of time scale and system-size of simulations are a bottleneck when computations need to match experiments. With respect to the time scale, enhanced sampling methodologies, such as accelerated Molecular Dynamics (MD), allow routine access to millisecond events. However, for big-size systems, the configurational space sampling often results poorly explored, resulting in a large statistical noise, which makes difficult the derivation of well-converged free energy profiles.

With respect to the system-size, CG and MS methods enable the reduction of the degrees of resolution, reaching the (sub)cellular level by “coarse graining” at different resolution (AccChemRes 2010, 43, 220). CG leaves to the user the definition of the interacting centers, opening issues regarding the models parameterization. MS models extremely coarse the system with the need to ensure accuracy re-including the relevant internal degrees of freedom. As such, MS (and CG) models are being integrated with non-particle approaches (elastic networks, continuum membrane models), invading the domain of bioengineering. This allows reaching the μm domain with relatively modest computational resources and opens the road to integrative approaches including system biology and bioinformatics, linking molecular modeling and bioengineering. The reliability of these methods with respect to cryo-EM and electron tomography is a main open challenge, which is being addressed by considering multiple strategies, with inclusion of the experimental information via machine learning approaches or by exploring the vast conformational space available to individual interacting proteins using Monte Carlo or MD techniques (AnnuRevBiophys 2016, 5, 253). Finally, integrative methods revealing the architecture of large molecular complexes and cellular portions (e.g., IMP, Haddock, CellPACK) are going to be interfaced with atomic-level codes. Following the philosophy of “multiscaling”, by re-including the atomistic representation into the supra-molecular description, this is thought to drive one of the next-years challenges in biophysics, which is the simulation of the cellular components.

Overall, our workshop will touch all the major unresolved aspects that today represent the challenges in multiscale modeling, fostering discussion between leaders in the field and young scientists, with the aim of advancing the field and develop new computational tools for the future of biophysics.

Workshop description

Our workshop will revolve on three specific goals, as detailed below.

1. Towards longer time scales.
This section is dedicated to the time scale problem. Although enhanced sampling methods and BD allow sampling configurations over milliseconds and seconds, much has to be done such that computational data could match time-resolved experiments (FRET, NMR). We will focus on the need of developing rigorous reweighting algorithms, usually suffering from large statistical noise, for obtaining meaningful equilibrium data and energy landscapes from enhanced sampling simulations. We will also discuss the current challenges in simulating long-time scale processes, such as diffusion and macromolecular associations, via BD. While novel BD implementations have shown to overcome the rigid-body approximation, user-defined parameters controlling solvent dielectric, hydrodynamics, desolvation, and ion screening can affect the realism of the solvent model and the consistency of the result with respect to kinetic data.

2. Extending the system-size beyond the atomistic representations.
This section focuses on extending the system-size by using methods beyond atomistic representations, such as CG and MS, for higher or lower resolution, respectively. These methods, which enable the description of supra-molecular structures (viruses, organelles, synaptic vesicles), will be discussed in light of their combination with non-particle methods such as continuum membrane, which is a frontier topic. Issues arise from the inclusion of the membrane elasticity and to its interaction with the particle-like representation of the cytoplasm, as well as when diffusion of membrane proteins has to be considered. Additional issues arise from the development of methods enabling the construction of large-scale models of membranes including curvatures. These problems are under debate and will be discussed in this workshop.

3. Multiscale modeling toward the simulation of the cell.
Here, we will discuss the integration of MS and bioengineering methods to realize large-scale models of the cell. Models of large biomolecular complex and cellular components obtained by CG-MS modeling supported by Cryo-EM data will be combined by means of integrative algorithms, incorporating data from systems biology and structural biology to provide models of (sub)cellular architectures. The reliability of these methods with respect to cryo-EM and electron tomography is a main open challenge, which is to be addressed by considering as a linear combination the physico-chemical properties of the system (with particular attention to inter-macromolecular binding affinity), or by using machine learning approaches on a large amount of heterogeneous data. Ongoing efforts are in extending the capabilities of these algorithms to create full-scale atomic-level models that can be used as input for MD simulations. Attention will be given to these open challenges, while also disussing the integration of these algorithms with the BD and with the Adaptive Poisson Boltzmann Model (APBS) software, for enabling to compute diffusion processes at the cellular level.

2 Program

Day 1 - Monday February 4th, 2019

- 08:00 to 08:30 – Welcome and Introduction

Mixing resolutions – Chair: Alexandre Bonvin

- 08:30 to 09:10 – **Martin Zacharias**
  Combining coarse-grained and atomistic models to exploring bio-molecular interactions
- 09:10 to 09:50 – **Ursula Roethlisberger**
  TBA
- 09:50 to 10:05 – **Natalia Ostrowska**
  Effect of crowding on the dynamics of the hepatitis C virus protease NS3/4a
- 10:05 to 10:20 – Coffee Break
- 10:20 to 11:00 – **Angelo Rosa**
  Coarse-grained computer simulations of eukaryotic chromosomes
- 11:00 to 11:40 – **Walter Rocchia**
  Continuum–based models for the description of mesoscale systems: from the molecular surface to chromatin compaction

- 11:40 to 12:20 – **Round Table – Led by Joanna Trylska**
- 12:20 to 14:00 – Lunch

The large scales: simulating diffusion and macromolecular associations – Chair: Matteo Dal Peraro

- 14:00 to 14:40 – **Rebecca Wade**
  Towards computationally efficient approaches to study drug binding kinetics
- 14:40 to 15:20 – **Alessandra Magistrato**
  Atomic-level simulations of splicing: catalytic mechanism and its functional modulation by the protein environment
- 15:20 to 15:40 – Coffee Break
- 15:40 to 16:20 – **Joanna Trylska**
  Simulating transport of vitamin B12 and its conjugates with peptide nucleic acids through the E. coli outer membrane receptor
- 16:20 to 17:00 – **Helmut Grubmuller**
  Atomistic Simulation of Biomolecular Function: Ribosomal Translation, Ligand Binding Heterogeneity, and a Dynasome Perspective
- 17:00 to 17:40 – **Gary Huber**
  Brownian Dynamics and Multiscale Modeling

- 18:00 to 20:00 – **Poster Session**

Day 2 - Tuesday February 5th, 2019

Towards the extreme scales: landscape sampling, embedding, scalability – Chair: Giulia Palermo

- 08:30 to 09:10 - **Paolo Carloni**
  Neuronal G-protein coupled receptors: insights from multi-scale molecular simulation
- 09:10 to 09:25 – **Soundhararajan Gopi**
  Simulation of Long Time-Scale Events by Phase Space Reduction
- 09:25 to 09:40 – **Hender Lopez**
  Short-time diffusive dynamics of proteins in a naturally crowded environment
- 09:40 to 09:55 – **Jean-Philip Piquemal**
  Scalable polarizable molecular dynamics using Tinker-HP: millions of atoms on thousands of cores
- 09:55 to 19:10 – Coffee Break
- 10:10 to 10:50 – **Michele Cascella**
  Simulating biological systems coupling particles and fields with molecular dynamics
- 10:50 to 11:30 – **Zaida Luthey-Schulten**
  Towards simulating a minimal cell: integration of experiment and theory
- 11:30 to 11:45 – **Clarisse Ricci**
  Tailoring the Variational Implicit Solvent Method for New Challenges: Heterogeneous Hydration in Biomolecular Recognition

- 11:45 to 12:25 – **Round Table – Led by Gregory A. Voth**
- 12:25 to 14:00 – Lunch

Perspectives and challenges of Coarse Grained and Mesoscale models – Chair: Valentina Tozzini

- 14:00 to 14:40 – **Gregory A. Voth**
  Recent advances in Coarse Graining
- 14:40 to 15:20 – **Siewert J Marrink**
  Modeling Complex Cell Membranes
- 15:20 to 15:40 – Coffee Break
- 15:40 to 16:20 - **Giorgia Brancolini**
  Coarse Grained and Multi-Scale Modelling of Nanoparticle-Protein Interactions
- 16:20 to 17:00 – **Stefano Vanni**
  Towards a molecular view of lipid droplet biogenesis
- 17:00 to 17:40 - **Thomas Steinbrecher**
  Mixed All-atom/Coarse-grained and Pure Coarse-grained Modeling for Drug Discovery
- 17:40 to 17:55 – **Benjamin Jagger**
  Drug Binding Kinetics with a Multiscale Milestoning Simulation Approach

- 18:00 to 20:00 – **Poster Session**
- 20:00 – **Social Dinner**

Day 3 - Wednesday February 6th, 2019

Beyond coarse graining: Integrative approaches – Chair: Rommie E. Amaro

- 08:30 to 09:10 – **Christian Micheletti**
  Privileged topologies of self-assembling molecular knots
- 09:10 to 09:25 – **Giovanni Pinamonti**
  Integrative Modelling of the Presynaptic Active Zone
- 09:25 to 09:40 – **Simon Olsson**
  Addressing accuracy and size limitations in models of molecular kinetics
- 09:40 to 10:00 – Coffee Break
- 10:00 to 10:40 – **Marco De Vivo**
  Monolayer protected gold nanoparticles, on the move: Toward nanoreceptors with intelligent recognition abilities
- 10:40 to 10:55 – **Deniz Aydin**
  Overcoming the hydrophobic barrier of the membrane: The role of COQ9 in promoting coenzyme Q biosynthesis
- 10:55 to 11:35 – **Holger Gohlke**
  TBA
- 11:35 to 11:50 – **Luca Monticelli**
  Lipid droplet budding: insight from molecular simulations

- 11:50 to 12:30 – **Round Table – Led by Paolo Carloni**
- 12:30 to 14:00 – Lunch

Towards longer time scales - The configuration space sampling challenge - Chair: Matteo Dal Peraro

- 14:00 to 14:40 – **Vittorio Limongelli**
  GPCRs dimerization unveiled by millisecond timescale free-energy calculations.
- 14:40 to 15:20 – **Steffen Lindert**
  Umbrella Sampling Simulations Elucidate Differences in Troponin C Isoform and Mutant Hydrophobic Patch Exposure
- 15:20 to 15:40 – Coffee Break
- 15:40 to 16:20 – **Ivaylo N. Ivanov**
  Molecular architecture and functional dynamics of the human transcription initiation machinery
- 16:20 to 17:00 – **Adrian Mulholland**
  Multiscale modelling of enzyme activity and inhibition for biocatalysis and drug development
- 17:00 to 17:40 –**Yinglong Miao**
  Enhanced sampling of G-protein-coupled receptor-G protein interactions

- 17:40 to 21:00 – **Conclusions and remarks**

3 Special Issue

Call for Papers

Multiscale Modeling from Macromolecules to Cell

Inspired by the workshop Multiscale Modeling from Macromolecules to Cell (CECAM Lausanne, Feb 4-6 2019), this paper collection aims at including an exhaustive discussion on old and new issues emerging in multi-scale modeling, especially as the method is pushed towards the macroscopic scales.

Learn more: frontiersin.org/research-topics/9704

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Guest Editors
Valentina Tozzini, Istituto Nanoscienze (CNR), Italy
Giulia Palermo, University of California, USA
Matteo Dal Peraro, EPFL, Switzerland
Alexandre M.J.J. Bonvin, Utrecht University, Netherlands
Rommie E. Amaro, University of California, USA

4 Abstracts

Modeling Complex Cell Membranes

S.J. Marrink[1]

1. University of Groningen, The Netherlands

In this lecture I will describe our current efforts to capture the dynamic organization of cell membranes, based on the coarse-grain Martini model developed in our lab [1]. I will illustrate the power of the model by providing a few in-depth examples of large-scale simulations involving membranes with realistic composition, in particular, the lateral organization of lipids and proteins in complex plasma membrane models [2,3]. Finally I will discuss details of the new Martini 3.0 release, and our aims for the future development.

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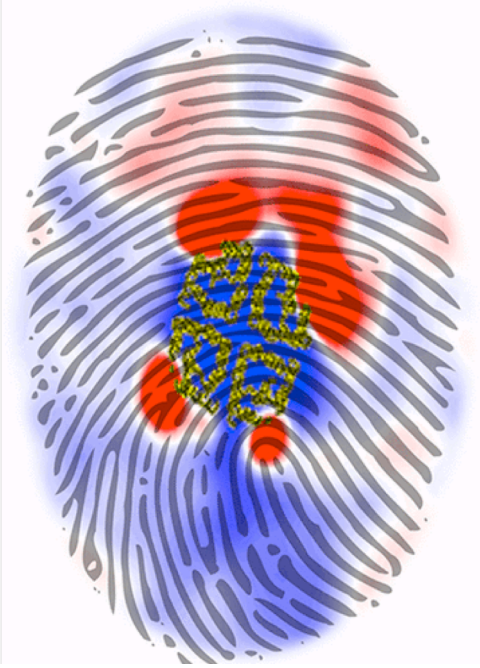

Figure 1. Proteins embedded in a realistic plasma membrane show distinct protein-lipid interaction patterns. These 'fingerprints' are fundamental to the lateral organizational principles of cell membranes.

Email: s.j.marrink@rug.nl

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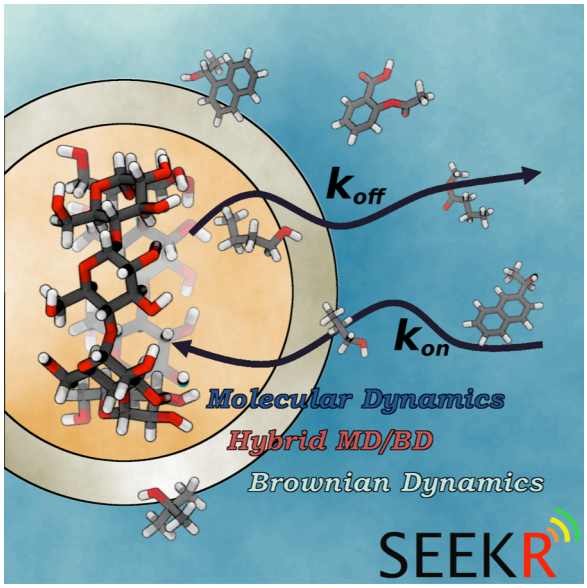
Drug Binding Kinetics with a Multiscale Milestoning Simulation Approach

Benjamin Jagger[1]

1. University of California San Diego (USA)



Molecular binding events are a fundamental aspect of cellular processes and are therefore of particular interest for the development of novel therapeutics. Efficient prediction and ranking of small molecule binders by their kinetic (kon and koff) and thermodynamic (ΔG) properties can be a valuable metric for drug lead optimization, as these quantities are often indicators of in vivo efficacy.1–3 Simulation based approaches that can efficiently estimate these quantities are desirable because they can provide critical detail at the molecular level and offer opportunities for lead optimization. We present recent developments to our multiscale molecular dynamics, Brownian dynamics, and milestoning software for estimating protein-ligand association and dissociation rates as well as binding thermodynamics, called "Simulation Enabled Estimation of Kinetic Rates" (SEEKR).4,5 Milestoning theory provides the glue for the multiscale scheme by providing a strategy to subdivide, simulate, and subsequently statistically reconnect small regions of simulation space called "milestones".6,7 This approach reduces the compute time required to simulate transition events, is embarrassingly parallel, and is agnostic to the simulation modality used. This allows us to use atomically detailed, yet computationally expensive, fully flexible MD simulations in milestones near the binding site where these interactions are critical for understanding the binding and unbinding, and BD simulations far from the binding site where rigid body dynamics provides a sufficient description at significantly reduced computational cost. We describe the effectiveness of the approach for rank-ordering ligands by dissociation rates and binding free energies for a model host-guest system, as well as the successful calculation of kinetics for protein-ligand systems. We also describe improvements to SEEKR focused on making such calculations feasible for larger systems of pharmaceutical relevance. These improvements include implementation changes to reduce simulation cost and on-the-fly convergence monitoring.

Email: bjagger@ucsd.edu

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GPCRs dimerization unveiled by millisecond timescale free-energy calculations

Vittorio Limongelli[1]

1. Faculty of Biomedical Sciences, Institute of Computational Science, University of Lugano USI (Switzerland)
2. Faculty of Pharmacy, University of Naples "Federico II" (Italy)

Membrane proteins diffuse in the phospholipid bilayer forming functional dimers and oligomers which can play specific roles during cell cycle and in pathological condition. Unfortunately, the elucidation of membrane protein/protein binding interaction is difficult using standard experimental and computational techniques because of the size and complexity of the systems, and the slow diffusion of proteins in membrane. In the present talk, I introduce an innovative multiscale approach that combines Coarse-Grained molecular dynamics and MetaDynamics (CG-MetaD) [1], allowing to overcome both the size and the timescale limit of the state-of-the-art techniques. Specifically, in CG-MetaD the representation of the system as beads instead of atoms reduces the dimensionality of the system under investigation, while metadynamics enhances the phase space exploration, allowing practical investigation of long timescale and large-scale motions of proteins in membrane. As a result, CG-MetaD super-accelerates the sampling allowing to go over the second timescale, well beyond the timescale accessible by the state-of-the-art simulations.

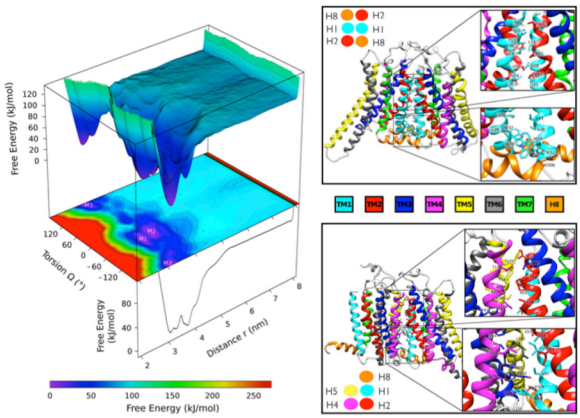

Figure 1. The free energy surface of the A2A GPCR dimerization (left) with the lowest energy dimer states (right)

CG-MetaD has been used to disclose the free energy landscape underlying the dimerization mechanism of the transmembrane helices of the epidermal growth factor receptor. The characterization of the free energy minima allows identifying the active and inactive conformations of the receptor, shedding light on possible activation pathways [1]. Very recently, we have performed millisecond CG-MetaD calculations to describe the dimerization process of the chemokine GPCRs, CCR5 and CXCR4, and the adenosine GPCRs, A2A and A2B. The free diffusion of the proteins in membrane and the occurrence of several protein/protein binding events during the simulation, lead to a well-characterized free energy surface and the identification of the receptors' dimer states [2]. The dimerization interface in all the energy minima is characterized with atomistic resolution, elucidating the involvement of lipids and cholesterol molecules. Our findings pave the way to further investigations, especially drug design, in which the dimer states might be targeted to discover ligands able to interfere with the chemokine and adenosine GPCRs dimer formation that characterizes severe pathologies like neurodegenerative disorders, cancer and HIV.

Email: vittoriolimongelli@gmail.com

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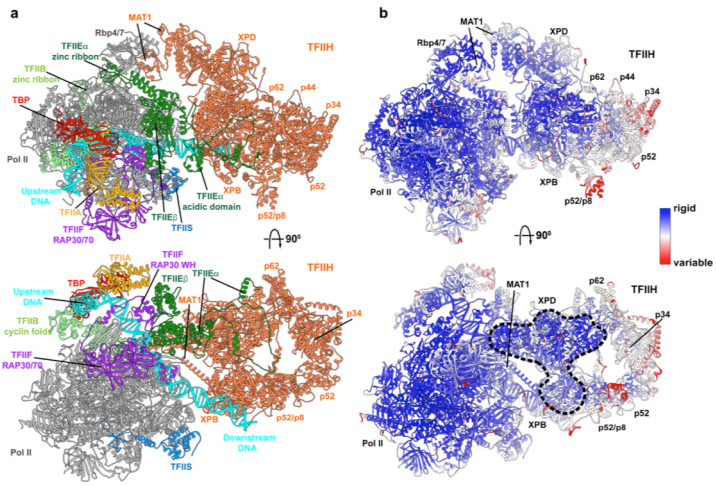
Molecular architecture and functional dynamics of the human transcription initiation machinery

Ivaylo Ivanov[1], Chunli Yan[1], Thomas Dodd[1]

1. Department of Chemistry, Georgia State University, Atlanta, GA, United States



Transcription regulation ultimately underlies cell differentiation, organism development and all cellular responses to environmental change. Yet, the molecular architecture and functional dynamics of the transcription initiation machinery are still incompletely understood. Here we synthesize available cryo-EM data to produce the most complete atomistic model of the human transcription pre-initiation complex (PIC) to date, including the ten-subunit general transcription factor TFIIH and its flexible kinase (CAK) module. The overall conformation of the assembly has been flexibly fitted into the EM density of the closed complex holo-PIC. The quality of our new models makes them suitable for molecular dynamics (MD) simulations on massively parallel computing platforms. Thus, we carried out extensive MD simulations to unveil the functional dynamics of Pol II holo- and core-PICs. To our knowledge, this is the first molecular simulation of the human transcription initiation machinery. Our analysis unveiled the hierarchical organization of the PIC machinery into dynamic communities and explained how its numerous structural elements function together to remodel the DNA substrate and facilitate promoter opening. The structure of the newly discovered allosteric modules and networks within TFIIH are in perfect correspondence with existing TFIIH mutational data from in vitro experiments and from disease-associated patient mutations. Thus, the present study provides a conceptual basis to rationalize a significant body of experimental evidence on the etiology of inherited genetic disorders such as xeroderma pigmentosum (XP) and trichothiodystrophy (TTD). In addition, our models provide a structural framework for future experiments aimed at unraveling the intricate molecular choreography of transcription initiation.

Email: iivanov@gsu.edu

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Ursula Roethlisberger

1. Laboratory of Computational Chemistry and Biochemistry, Institute of Chemical Sciences and Engineering, École Polytechnique FeďeŕaledeLausanne,CH-1015Lausanne, Switzerland

TBA

Email: ursula.roethlisberger@epfl.ch

Towards computationally efficient approaches to study drug binding kinetics

Rebecca C. Wade[1,2]

1. Molecular and Cellular Modeling Group, Heidelberg Institute for Theoretical Studies (HITS), Schloss-Wolfsbrunnenweg 35, 69118 Heidelberg, Germany
2. Zentrum für Molekulare Biologie (ZMBH), DKFZ-ZMBH Alliance and Interdisciplinary Center for Scientific Computing (IWR), Heidelberg University, Germany

Growing evidence that the efficacy of a drug can be correlated to target binding kinetics has led to the development of many new methods aimed at computing rate constants for receptor-ligand binding processes [1], see also: kbbox.h-its.org. Here, I will describe our studies to explore the determinants of structure-kinetic relationships (SKR), to investigate the effects of macromolecular crowding on the diffusion of drugs, and to develop computationally efficient methods to estimate drug-target binding kinetic parameters.

We address the challenges of computing drug-target residence times with τ-random acceleration molecular dynamics simulation (τRAMD) to compute relative residence times [2] and with Comparative Binding Energy (COMBINE) Analysis to derive QSKRs from structures of ligand-receptor complexes [3]. We demonstrate the application of these approaches to a set of 70 diverse drug-like HSP90 ligands [4], obtaining good agreement with experiment, and identifying features that affect ligand unbinding rates, including transient polar interactions and steric hindrance.

To study drug-target association, we employ a combination of Brownian and molecular dynamics simulations. We apply Brownian dynamics (BD) simulations, as implemented in the Simulation of Diffusional Association (SDA) 7 software [5], to investigate how the diffusion rates of drug-like molecules are affected by the presence of protein crowders, and to compute rate constants for drug-target diffusional association. In the BD simulations, the solutes are represented by one or more rigid conformations. To account for conformational gating of ligand binding, we employ MD simulations and Markov state models to define distinct conformers that are sampled during BD simulations of ligand association. We describe application of this approach to a set of inhibitors of the conformationally flexible protein, HIV-1 protease.

Email: rebecca.wade@h-its.org

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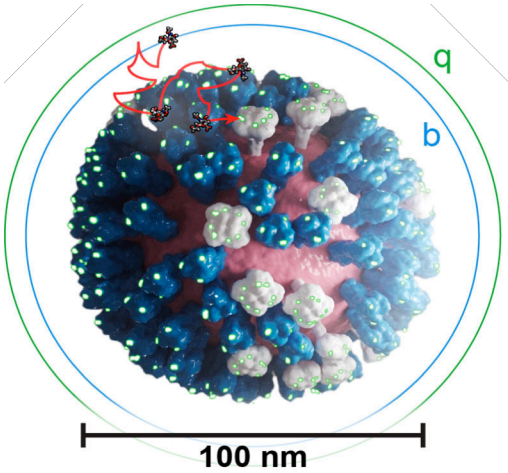
Brownian Dynamics and Multiscale Modeling

Gary Huber[1]

1. Department of Chemistry and Biochemistry, University of California San Diego

This talk will discuss the software package Browndye 2.0 for Brownian dynamics, various applications, and some of the algorithms implemented and under development. Browndye's main area of concentration is in computing rate constants and transition probabilities for assemblies of modest numbers of large molecules, with adjustable levels of detail. In addition to discussing the particulars of the package, we will discuss how BD simulation algorithms can be used to extend the length and time scales of biological simulations.



Browndye Website: https://browndye.ucsd.edu

Email: gahuber95@gmail.com

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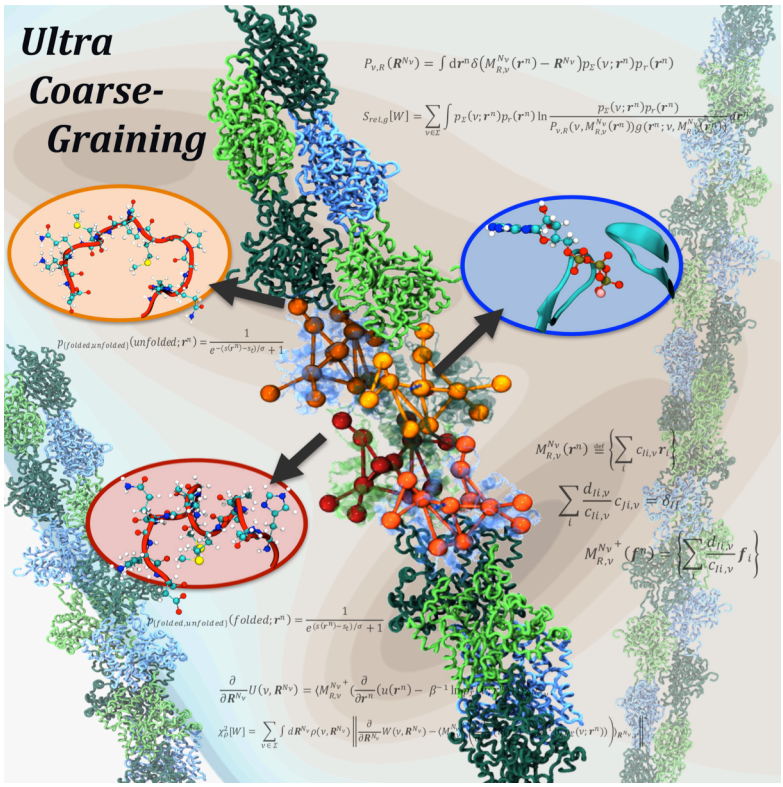
Recent Advances Coarse-graining

Gregory Voth[1]

1. Department of Chemistry, James Franck Institute, and Institute for Biophysical Dynamics, The University of Chicago, Chicago, IL, USA



Advances in theoretical and computational methodology will be presented that are designed to simulate complex (biomolecular and other soft matter) systems across multiple length and time scales. The approach provides a systematic connection between all-atom molecular dynamics, coarse-grained modeling, and mesoscopic phenomena. At the heart of these concepts are methods for deriving coarse-grained (CG) models from molecular structures and their underlying atomic-scale interactions. This particular aspect of the work has strong connections to the procedure of renormalization, but in the context of CG models it is developed and implemented for more heterogeneous systems. Recent advances in comparing and synthesizing multiscale coarse-graining (MS-CG, aka "force matching") and relative entropy minimization will be presented, along with methods to rigorously introduce "virtual" CG site to represent, e.g., the effects of solvent implicitly. An important new component of our work has also been the concept of the "ultra-coarse-grained" (UCG) model and its associated computational implementation. In the UCG approach, the CG sites or "beads" can have internal states, much like quantum mechanical states. These internal states help to self-consistently quantify a more complicated set of possible interactions within and between the CG sites, while still maintaining a high degree of coarse-graining in the modeling. The presence of the CG site internal states greatly expands the possible range of systems amenable to accurate CG modeling, including quite heterogeneous systems such as aggregation of hydrophobes in solution, liquid-vapor and liquid-solid interfaces, and complex self-assembly processes such as occurs for large multi-protein complexes. Finally, a new bottom-up method for mapping atomistic to mesoscopic models will be described as time allows.

Email: gavoth@uchicago.edu

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Combining coarse-grained and atomistic models to exploring biomolecular interactions

Martin Zacharias[1]

1. Physics Department, Technical University Munich James Franck Str. 1, D-85747 Munich

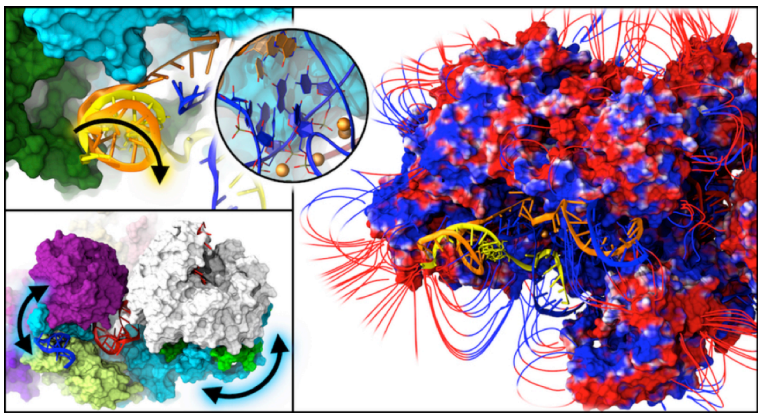
Most biological processes are mediated by protein-protein or protein-nucleic acid interactions. Structural modeling and docking of biomolecules is of importance allowing to generate structural models of dimeric and multimeric biomolecular complexes. We have developed the Attract protein-protein docking approach employing a coarse-grained protein and nucleic acid force field that allows rapid modeling and evaluation of complexes. The approach accounts approximately for local and global conformational changes during association. It is possible to efficiently account for experimental information from various sources including low resolution CryoEM data to guide structural modeling. Efforts to extend and improve the approach and to translate between scales for modeling large biomolecular assemblies will be presented. In order to translate predicted complexes on the coarse-grained level and to optimize the refinement and evaluation of structural models we have developed new atomistic approaches that will also be discussed.

Email: martin.zacharias@mytum.de

Atomic-level simulations of splicing: catalytic mechanism and its functional modulation by the protein environment

Alessandra Magistrato[1]

1. CNR-IOM and International School for Advanced Studies, Trieste. Italy



The spliceosome biology is currently undergoing a revolutionary phase due to increasing number of the cryo-EM structures at near-atomistic resolution recently solved. The presence of non-coding sequences (introns) in nascent RNA transcripts is a hallmark of the genomes of all organisms. Understanding the mechanism of splicing (i.e. introns removal before protein translation) is of utmost importance since aberrant splicing is associated to numerous complex diseases.
The spliceosome carries out splicing in eukaryotes in two subsequent reactions, mediated by Mg2+ ions, undergoing a series of compositional and conformational changes. In this talk I will initially elucidate how splicing occurs in group II introns, Mg2+-dependent ribozymes considered to be the evolutionary ancestors of the eukaryotic spliceosome. By employing hybrid quantum–classical QM(Car–Parrinello)/MM molecular dynamics (MD) simulations we elucidated the molecular mechanism of the first and rate- determining step of the splicing process catalyzed by these ribozymes [1]. Moving from the bacteria ribozyme to yeast spliceosome we took advantage of all-atom classical MD simulations to disentangle the functional dynamics of two spliceosome complexes: (i) the intron lariat spliceosome (ILS) from S. Pombe, which corresponds to the final step of the splicing cycle. Multiple microseconds-long MD simulations of a 700000 or 1000000 atoms model in explicit water revealed how conformational plasticity modulates the properties of the RNA catalytic core, affects molecular recognition of the splicing site [2]; (iii) we then investigated how spliceosome mutations implicated in hematologic malignancies alter the functional dynamics of one splicing factor (Hsh155) contained in the Bact complex from yeast S. cerevisiae. This affects the binding and the selection of two key intron recognition sites: branch point sequence (BPS) and the 3'splice site, resulting in aberrantly spliced RNA transcripts.
Besides contributing to the fundamental understanding of the spliceosome structural and functional biology, our study provides valuable information to harness splicing for revolutionary gene modulation tools and novel therapeutic approaches.

Email: alema@sissa.it

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Monolayer protected gold nanoparticles, on the move: Toward nanoreceptors with intelligent recognition abilities

Marco De Vivo[1]

1. Molecular Modeling and Drug Discovery Lab, Istituto Italiano di tecnologia, Genova, Italy

The self-assembly of a monolayer of ligands on the surface of noble metal nanoparticles allows the realization of ordered and complex molecular structures, with applications that span from materials science and electronics, to bioimaging, nanomedicine and even catalysis. Here, we will show how molecular dynamics (MD) simulations of realistic 3D models built using our recently released NanoModeler webserver (www.nanomodeler.it), can help in characterizing, with unprecedented detail, the fundamental molecular mechanisms of binding pockets formed into the monolayer of monolayer-protected gold nanoparticles (AuNPs). Notably, NanoModeler is the first webserver designed to automatically generate and parameterize model systems of AuNPs and gold nanoclusters. Our extended simulations, integrated with experiments, explain the selectivity and sensitivity observed for different organic analytes in NMR chemosensing experiments. Thus, our findings advocate for the rational design of tailored coating groups to form specific recognition binding sites on monolayer-protected AuNPs. These may find applications for detecting small molecules such as drugs, metabolites, illegal drugs, and small molecular markers for cancer.

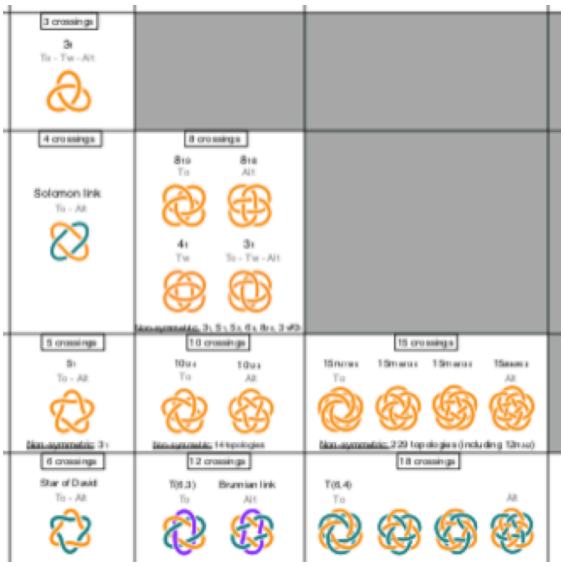
Email: marco.devivo@iit.it

Privileged topologies of self-assembling molecular knots

Cristian Micheletti[1]

1. International School for Advanced Studies (SISSA), Trieste, Italy

The self-assembly of objects with a set of desired properties is a major goal of material science and physics. A particularly challenging problem is that of self-assembling structures with a target topology. Here we show by computer simulation that one may design the geometry of string-like rigid patchy templates to promote their efficient and reproducible self-assembly into a selected repertoire of non-planar closed folds including several knots. In particular, by controlling the template geometry, we can direct the assembly process so as to strongly favour the formation of constructs tied in trefoil or pentafoil, or even of more exotic knot types. A systematic survey reveals that these "privileged", addresable topologies are rare, as they account for only a minute fraction of the simplest knot types. This knot discovery strategy has recently allowed for predicting complex target topologies [1,2,3[, some of which have been realized experimentally [4,5].



Email: michelet@sissa.it

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Holger Gohlke

1. Heinrich-Heine-Universität Düsseldorf, Institut für Pharmazeutische und Medizinische Chemie, 40225 Düsseldorf, Germany

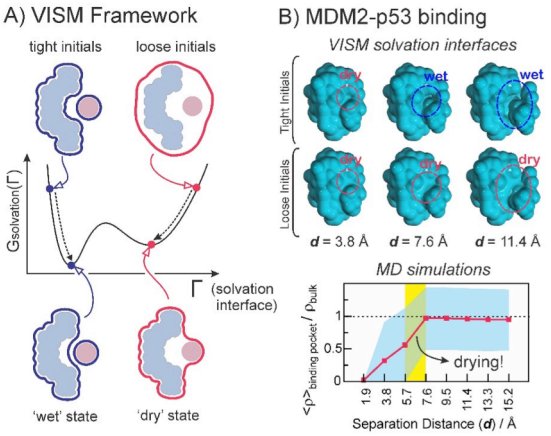
TBA

Email: gohlke@uni-duesseldorf.de

Tailoring the Variational Implicit Solvent Method for New Challenges: Heterogeneous Hydration in Biomolecular Recognition

Clarisse G. Ricci[1], Bo Li[2,3], Li-Tieng Cheng[2], Joachim Dzubiella[4], and J. Andrew McCammon[1]

1. Department of Pharmacology and Department of Chemistry & Biochemistry, National Biomedical Computation Resource, University of California at San Diego (UCSD), La Jolla, CA 92093, USA
2. Department of Mathematics, UCSD, La Jolla, CA 92093, USA
3. Quantitative Biology Graduate Program, UCSD, La Jolla, CA 92093, USA
4. Institut für Physik, Humboldt-Universität zu Berlin, D-12849, Berlin, Germany, and Soft Matter and Functional Materials, Helmholtz-Zentrum Berlin, D-14109, Berlin, Germany



Water, despite being a driving force in biochemical processes, has an elusively complex microscopic behavior. For instance, water can increase its local density near amphiphilic protein surfaces and also evaporate from hydrophobic surfaces and cavities, an effect known as 'dewetting'. While an atomistic, explicit description of water can be too expensive in large biomolecular systems, most implicit solvent methods fail to capture dewetting effects and heterogeneous hydration by relying on pre-established (i.e. *guessed*) solvation interfaces In contrast with such methods, the Variational Implicit Solvent Method (VISM) is an implicit solvent method that includes water 'plasticity' in the picture by formulating the solvation free energy as a functional of all possible solvation interfaces.[1] By minimizing this functional, VISM produces the solvation interface as an *output* of the calculations. Also, minimization of the VISM functional can lead to distinct solvation interfaces (depending on the initial guess), indicating the existence of multiple hydration states. Here, we describe how VISM is being tailored to deal with biological systems such as proteins, whose complex topology often produces heterogeneous hydration effects. Specifically, we show how VISM can correctly describe hydration in the molecular recognition of two distinctive protein-protein complexes – the hydrophilic barstar-barnase and the hydrophobic MDM2-p53 – in good agreement with atomistic, explicit solvent molecular dynamics simulations. Some of the most recent advances in the VISM framework include i) combining VISM with coarse-grained solute Hamiltonians adapted from the MARTINI framework[2] and ii) replacing the continuous level-set function currently used to describe the solvation interface by a simplified, binary level-set function that makes the VISM calculations several order of magnitude faster. The advances and results reported herein encourage us to combine VISM with molecular simulations to obtain a new biophysical method that is able to efficiently describe complex heterogeneous hydration in large biomolecular systems.

Email: cgravinaricci@ucsd.edu

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Coarse Grained and Multi-Scale Modelling of Nanoparticle-Protein Interactions

Giorgia Brancolini[1], S. Corni[1,2] and V. Tozzini[3]

1. CNR-NANO S3, Institute of Nanoscience, via Campi 213/A, 41100 Modena, Italy
2. Department of Chemical Science, University of Padova, via Marzolo 1, 35131 Padova, Italy
3. NEST-CNR, Institute of Nanoscience, P.zza San Silvestro 12, 56127 Pisa, Italy

Transcription We present the development of a specific Coarse Grained (CG) approach which combines the choice of the minimal possible resolution, coherency between different levels of resolution and a parameterization combining bottom-up and top down elements, to achieve an accurate descriptions of protein-surface systems. We combine a minimalist CG model (one-bead-per-amino acid) of a fibrillogenic protein, β2 microglobulin, with a Morse network model for a functionalized gold nanoparticle, $(Au_{25}[S(CH_2)_2Ph]_{18})^-$ which is know to lead to a potential inhibition of the fibrillation activity[1]. The novelty of the research proposal respect to the state-of-the-art, is the description and parameterization of protein-NP interaction based on data obtained from docking and enhanced sampling molecular dynamics including information about the diffusivity of the gold NPs and protein in solution.[2-3]

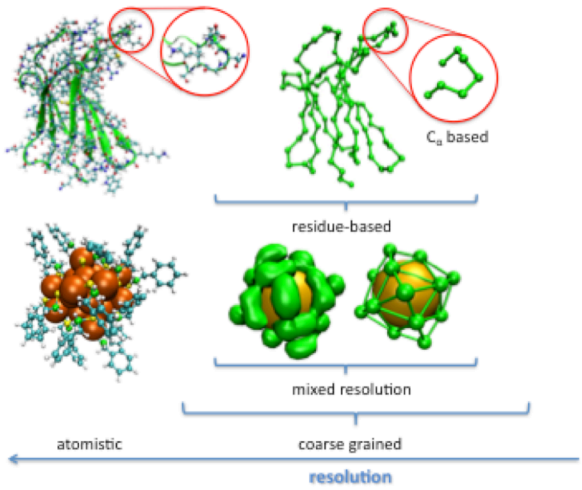

Figure 1. From left to right: atomistic representation (a protein and a functionalized gold nanoparticle in ball&sticks); in the center the residue–resolution level for the protein (Cα is represented in green) and for the NP (green balls are located on a position roughly corresponding to Cα of the functionalizing group, spatial distribution is also represented as green isodensity surface)

Email: giorgia.brancolini@nano.cnr.it

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Neuronal G-protein coupled receptors: insights from multi-scale molecular simulation

Paolo Carloni[1], S. Corni[1,2] and V. Tozzini[3]

1. Forschungszentrum Juelich GmbH

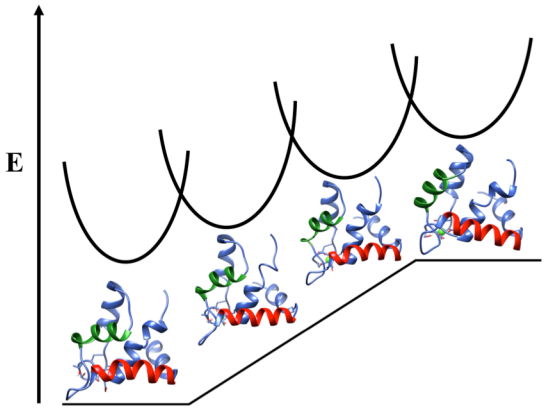
G-protein coupled receptors (GPCRs) are involved in a myriad of important processes for neuronal function and dysfunction. Here we will summarize some recent simulation studies on GPCRs of neuropharmaceutical relevance, aimed at advancing our molecular-level understanding of agonist binding and receptor activation.

Email: p.carloni@fz-juelich.de

Umbrella Sampling Simulations Elucidate Differences in Troponin C Isoform and Mutant Hydrophobic Patch Exposure

Steffen Lindert[1]

1. Department of Chemistry, Ohio State University, Columbus Ohio, United States



Troponin C (TnC) facilitates muscle contraction through calcium-binding within its N-terminal region (NTnC). This calcium-binding event leads to an increase in the dynamics of helices lining a hydrophobic patch on TnC. We applied umbrella sampling to probe the TnC hydrophobic patch opening in a targeted and quantitative fashion. We investigated the differences in the free energy of opening between cardiac (cTnC) and fast skeletal TnC (sTnC) and found that, in agreement with previous reports, holo (calcium-bound) sTnC had a lower free energy of opening compared with holo cTnC. Additionally, differences in the free energy of opening of hypertrophic (HCM) and dilated cardiomyopathy (DCM) cTnC systems were investigated. MD simulations and umbrella sampling revealed a lower free energy of opening for the HCM mutations A8V and A31S, as well as the calcium-sensitizing mutation L48Q. The DCM mutations, Y5H, Q50R, and E59D/D75Y, all exhibited a higher free energy of opening. An umbrella sampling simulation of cTnI-bound holo cTnC exhibited the lowest free energy in the open configuration, in agreement with experimental data. Additionally, the umbrella sampling protocol developed for studying HCM/DCM associated mutations, as well as molecular dynamics simulations, were used to investigate a potential mechanism of small molecules for altering calcium sensitivity. We were able to show that the addition of small molecules in the hydrophobic patch caused a lowering of the free energy of opening and a stabilization of a semi-open configuration. These methodologies for studying cTnC provide a holistic view of the dynamics and functions of cTnC facilitating a molecular understanding of cardiac muscle contraction.

Email: lindert.1@osu.edu

Simulating biological systems coupling particles and fields with molecular dynamics

Michele Cascella[1]

1. Department of Chemistry, and Hylleraas Centre for Quantum Molecular Sciences University of Oslo, Norway

The hybrid particle-field with molecular dynamics (hPF-MD) is a newly-established methodol- ogy based on density-functional potentials for the simulations of molecular systems [1]. Thanks to its low computational costs, hPF-MD is capable of treating large-scale soft matter systems us- ing relatively small high-performance architectures [2]. As case examples, I will first present the first hPF-MD model for peptides, showing how it is able to sculpt the main features of the fold- ing diagram for model hydrophobic-polar sequences [3]. Then, I will introduce advances in the fundamental electrostatic theory for density-field in both homogeneous and non-homogeneous dielectric [4]. This is a crucial ingredient to expand the application range of hPF-MD to gener- alised biological systems, which are characterized by a strong polar/ionic character. I will show how they can be effectively used to simulate polyelectrolytic systems like charged surfactants or polar-apolar mixtures [5].

Email: michele.cascella@kjemi.uio.no

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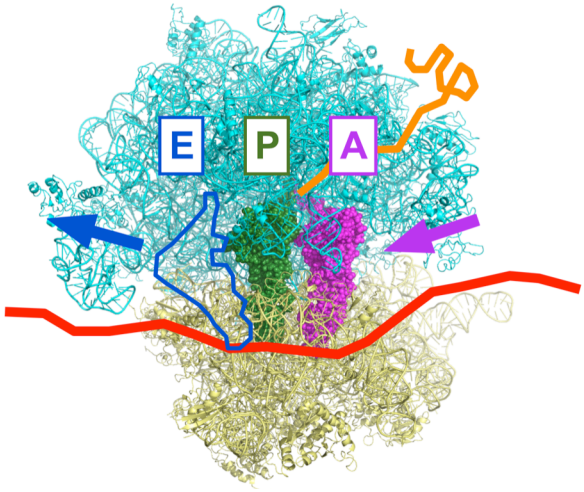
Atomistic Simulation of Biomolecular Function: Ribosomal Translation, Ligand Binding Heterogeneity, and a Dynasome Perspective

Lars V. Bock, Michal Kolar, Andrea C. Vaiana, Andreas Russek, Benjamin von Ardenne, **Helmut Grubmüller**

1. Max Planck Institute for Biophysical Chemistry, Theoretical and Computational Biophysics Department, Göttingen, Germany



Ribosomes are highly complex biological nanomachines which operate at many length and time scales. We combined single molecule, x-ray crystallographic, and cryo-EM data with atomistic simulations to elucidate how tRNA translocation, the action of antibiotics, and frameshifting work at the molecular level. We show that tRNA translocation between A, P, and E sites is rate limiting, and identified dominant interactions. We further describe a new combined allosteric mechanism for erythromycin-induced translational stalling of the antibiotics sensor peptide ErmB, as well as a free energy model that can explain and predict frameshifting efficiencies.
Using streptavidin/biotin as a model system with super-strong affinity, we show that the underlying free energy landscape which governs ligand binding and unbinding
can be extracted from combined atomic force microscopy (AFM) and force probe simulation data, which covers loading rates of 11 orders of magnitude. We will, finally, take a more global view on the 'universe' of protein dynamics motion patterns and demonstrate that a systematic coverage of this 'Dynasome' allows one to predict protein function.

Email: hgrubmu@gwdg.de

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Towards simulating a minimal cell: integration of experiment and theory

Zaida (Zan) Luthey-Schulten[1]

1. Department of Chemistry, NSF Center for the Physics of Living Cells, NIH Center for Macromolecular Modeling and Bioinformatics at the Beckman Institute, and the Carl Woese Institute of Genomic Biology, University of Illinois at Urbana-Champaign

Ribosomes---the primary macromolecular machines responsible for translating the genome into proteins---are complexes of precisely folded RNA and proteins. The ways in which their production and assembly are managed by the living cell is of deep biological importance. Our whole-cell model of ribosome biogenesis in a slowing growing bacteria includes the effects of growth, DNA replication, transcription, translation, ribosome assembly, and cell division. All biological processes are described in terms of reaction-diffusion master equations (RDME) and solved stochastically using the GPU-based Lattice Microbes simulation software over a cell cycle. The replication parameters are derived from single cell measurements of gene copy numbers in a series of E. coli strains with fluorescently labeled genes as a function of cell length and time. The work on biogenesis can now be linked with the essential metabolism of a minimal bacterial cell, JCVI-Syn3A. To treat processes at biologically relevant length- (microns), time- (hours), and concentration- (nanomolar to millimolar) scales requires hybrid RDME simulations. I will report on our efforts to develop a complete kinetic model of a minimal bacterial cell.

Email: zan@illinois.edu

Integrative Modelling of the Presynaptic Active Zone

Giovanni Pinamonti[1]

1. Freie Universität Berlin (Berlin, Germany)

The presynaptic active zone (see Fig. 1) is a crowded environment, where tens of different protein and protein-complexes cooperate for the efficient and accurate transmission of synaptic signals [1]. Our goal, is to gain insights on the structural details of the mechanism of neurosynaptic signal transmission, by properly combining experimental information with computational models.
We tackle this challenge from different directions. On one hand, we aim to model the structure of the Bruchpilot (BRP) protein, of Drosophila Melanogaster. This 1700 amino acids protein is known to cluster with other copies of itself into bundles which are involved in the synaptic vesicles recruitment. We employ coarse-grained simulations, combined with bioinformatic data extracted with direct-coupling analysis [2], and experimental results coming from yeast two-hybrid screening, cross-linking mass-spectrometry, and high-resolution STED microscopy. This enabled us to produce realistic models of different subunits of BRP, than can be combined together to obtain a model of a full bundle.
Additionally, we study the assembling of Soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) protein complex, a fundamental step in neuronal exocytosis [3]. During its folding SNARE is believed to visit multiple intermediate states, which have a crucial function in the regulation of the exocytosis process. We used a structure-based coarse-grained model to simulate the unzipping of SNARE under the action of a mechanical force, characterizing the structure and thermodynamic properties of multiple partially unfolded configurations (See Fig. 1), fully consistent with data coming from optical tweezers experiments, FRET analysis, and X-ray crystallography.

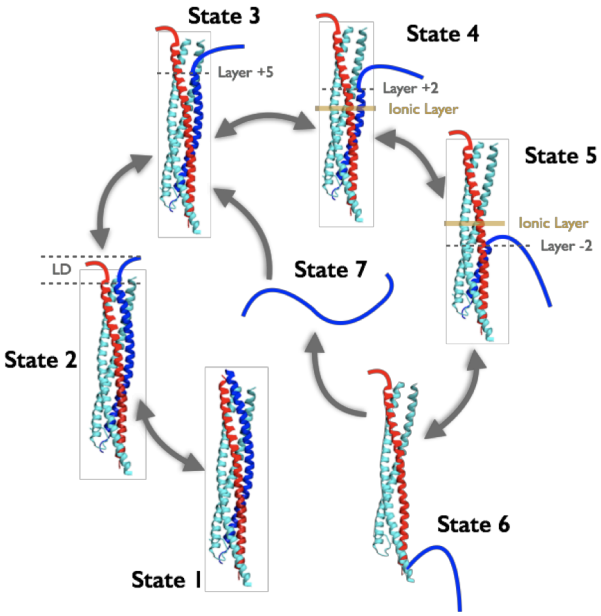

Figure 1. The intermediates in the assembling of the SNARE complex.

Email: giopina88@gmail.com

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Multiscale modelling of enzyme activity and inhibition for biocatalysis and drug development

Adrian Mulholland[1]

1. Centre for Computational Chemistry, School of Chemistry, University of Bristol, Bristol BS8 1TS, UK

Drug action is inherently a multiscale problem, connecting chemical changes at the molecular level with macroscopic biological changes [1]. Multiscale simulation methods have the potential to contribute to drug development by connecting models at different scales and to analyse the connections across scales, e.g. how changes on one scale lead to changes at another. Molecular simulation methods of various types are now capable of modelling processes ranging from biochemical reactions to membrane assembly, and offer increasing predictive power. Simulations can provide effective 'computational assays' of biological activity [2]. For example, classical molecular dynamics (MD) simulations can allow predictions of substrate binding, and reveal and predict dynamical changes associated with thermoadaptation and temperature optima of enzyme catalytic activity [3]. Increasingly, simulations are contributing to the design and engineering both of natural enzymes and of de novo biocatalysts [4]. Different types of application require different levels of treatment, which can be effectively combined in multiscale models to tackle a range of time- and length-scales, e.g. to study drug metabolism by cytochrome P450 enzymes [5], combining coarse-grained and atomistic molecular dynamics simulations, and combined mechanics/molecular mechanics (QM/MM) methods. QM/MM methods are themselves an archetype of multiscale methods in biochemistry. QM/MM methods treat the active site with a QM electronic structure method, while the effect of the environment is included by a simpler atomistic (MM) approach. QM/MM methods can be used e.g. for modelling transition states and reaction intermediates, to elucidate reaction mechanisms, to identify catalytic interactions, and to analyse structural and electronic determinants of reactivity. QM/MM modelling can identify mechanisms of catalysis in biosynthesis and antibiotic resistance, for example [6]. Projector-based embedding techniques allow highly accurate correlated ab initio QM methods to be applied in QM/MM calculations [7]. Multiscale simulation schemes also now allow QM/MM methods to be applied to free energy simulations to study e.g. protein-ligand binding [8]. Together with enhanced sampling simulations, QM/MM methods can help identify causes of drug resistance e.g. to targeted covalent inhibitors such as the lung cancer drug osimertinib [9] and the mechanism-based β-lactamase inhibitor clavulanate [6].

Email: adrian.mulholland@bristol.ac.uk

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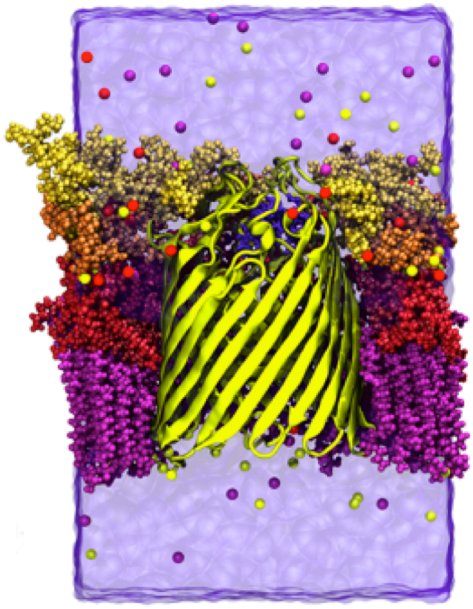
Simulating transport of vitamin B12 and its conjugates with peptide nucleic acids through the E. coli outer membrane receptor

Joanna Trylska[1]

1. Centre of New Technologies, University of Warsaw, Poland

Vitamin B12 (or cobalamin) is an essential enzymatic cofactor either produced or taken up by bacterial cells. The first stage of its uptake to Gram-negative E. coli cells occurs through the outer-membrane receptor protein termed BtuB. Vitamin B12 binds strongly and specifically to the extracellular side of this transmembrane protein. On the periplasmic side of the outer-membrane, BtuB interacts with the inner-membrane TonB protein, which leads to unfolding of the BtuB luminal domain and release of vitamin B12 to the periplasm.Peptide nucleic acid (PNA) is a synthetic DNA mimic. PNA oligomers are used to sequence-specifically block DNA or RNA in various biotechnology applications. PNA is not readily taken up by bacteria but we have experimentally found that conjugation of vitamin B12 to a PNA oligomer makes PNA enter E. coli cells [1].

Knowing that the transport of the PNA with vitamin B12 as a carrier does occur, we have been exploring various enhanced sampling techniques in molecular dynamics simulations to simulate the mechanism of transport of the above ligands through the BtuB receptor. For the simulations we built an asymmetric and heterogenous E. coli membrane model around the BtuB structure. We found that indeed transport of the vitamin B12-PNA conjugate is mechanically possible but requires large conformational change of the PNA oligomer. We observed that the otherwise compact structure of PNA [2,3] extends inside the BtuB receptor allowing for PNA passage. Therefore, as also supported by our experimental evidence, we suggest that vitamin B12-PNA conjugates may be transported through the BtuB protein in the E. coli outer membrane.



Email: jtrylska@ucsd.edu

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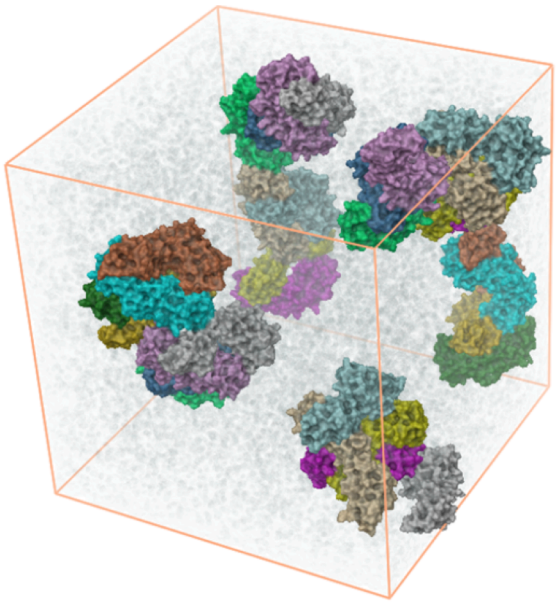
Mixed All-atom/Coarse-grained and Pure Coarse-grained Modeling for Drug Formulation

Thomas Steinbrecher,[1] John Shelley[1]

1. Schrodinger Inc. 120 West 45th Street 17th Floor, New York, NY 10036-4041



Association of solute molecules in solution occurs and affects the performance of many drugs in processing, storage and delivery. Amino-acid based drugs, such as oligopeptide, proteins and antibodies are particularly prone to problems from association due to their design and the high concentrations of the active ingredient that are often required. We describe complementary technologies that are relevant for the formulation of peptides. The first is a recently developed mixed all-atom/coarse-grained approach (AACG) for modeling fully flexible peptides in aqueous solution.1 We describe the application of this model to the aggregation of melittin, one of the most extensively studied oligopeptides, as a leading study involving peptide flexibility and association. This model is also applied to a full globular protein, lysozyme yielding suggestive results that are never-the-less limited by the time-scales and system size that can be studied with this fairly detailed approach. We are just starting to explore purely coarse-grained technologies that involve applying either Martini or DPD simulation approaches to study the self-assembly of larger aggregates at the expense of predictably modeling specific conformational changes.

Email: thomas.steinbrecher@schrodinger.com

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Towards a molecular view of lipid droplet biogenesis

S. Vanni[1], V. Zoni[1], P. Campomanes[1], R. Khaddaj[1], A.R. Thiam[2], R. Schneiter[1]

1. Department of Biology, University of Fribourg
2. Ecole Normale Superieure, Paris

Intracellular lipid droplets (LDs) are the main cellular site of metabolic energy storage and they are thus crucially involved in lipid metabolism. Besides their metabolic functions, however, LDs also play a central role in numerous processes, including lipotoxicity, cancer development, endoplasmic reticulum (ER) stress, viral attack or metabolic disorders, and they serve as platform for protein and lipid transport.
Despite the multiple functions of LDs in the cell, a basic understanding of their molecular properties is still missing, mostly because of their unique structure: a core of esterified fatty acids and sterols surrounded by a single monolayer of phospholipids (with sizes typically around 100 nm-µm), that makes them, in essence, intracellular oil emulsions stabilized by naturally-occurring phospholipids as surfactants.
Here we present recent results on the molecular mechanism of LD biogenesis using both existing and newly-developed methodologies based on molecular dynamics (MD) simulations. Using these approaches, we could identify the relevant parameters driving the spontaneous phase separation between triglycerides and phospholipids, leading to the formation of oil lenses in the ER bilayer and their subsequent budding via a dewetting mechanism.

Email: stefano.vanni@unifr.ch

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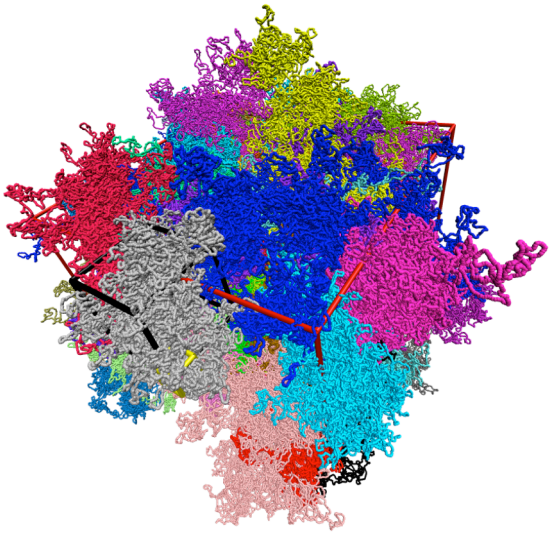
Coarse-grained computer simulations of eukaryotic chromosomes

Angelo Rosa[1]

1. Scuola Internazionale Superiore di Studi Avanzati (Sissa/Isas)

In this talk, I will review my work on the physical modeling of eukaryotic chromosomes. In particular, I will present results of detailed molecular dynamics computer simulations of a minimalistic coarse-grained polymer model which is able to reproduce with great accuracy the large-scale features of chromosomes, like their confinement to specific regions of the nucleus (territories) and the formation of contacts. The talk will be concluded by a discussion focusing on the conceptual connection between nuclear chromosome organization and the physics of untangled ring polymers in concentrated solutions.



Email: anrosa76@gmail.com

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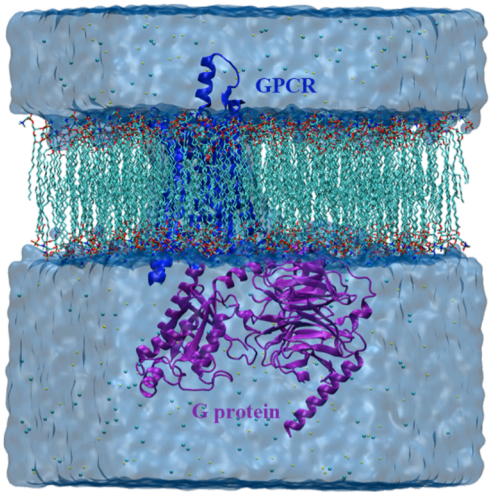
Enhanced sampling of G-protein-coupled receptor-G protein interactions

Yinglong Miao[1], Jinan Wang,[1] Apurba Bhattarai[1]

1. Center for Computational Biology and Department of Molecular Biosciences, University of Kansas, Lawrence, KS 66047



G-protein-coupled receptors (GPCRs) are the largest superfamily of human membrane proteins and serve as primary targets of ~1/3 of currently marketed drugs. Four subtypes of adenosine receptors, the A1, A2A, A2B, and A3, mediate a broad range of physiological functions. They have emerged as important therapeutic targets for treating cardiac ischemia, neuropathic pain and cancer. During function, the A1 and A3 receptors preferentially bind the Gi/o proteins, while the A2A and A2B receptors preferentially bind the Gs proteins. Moreover, the GPCR–G protein interactions are modulated by allosteric ligands. These ligands bind to a putative extracellular site of adenosine receptors with divergent sequences and conformations and have emerged as promising candidates as selective GPCR drugs. To date, adenosine receptors are the sole subfamily of GPCRs that have X-ray or cryo-EM structures determined in complex with distinct G proteins, i.e., the A1 and A2A receptors coupled with the Gi and Gs proteins, respectively. Here, we have performed all-atom enhanced simulations using a robust Gaussian accelerated molecular dynamics (GaMD) method on the GPCR-G protein complexes, as well as binding of prototypical allosteric modulators to the adenosine receptors. The GaMD simulations have revealed important insights into dynamic mechanisms of allosteric modulation of adenosine receptors and specific GPCR–G protein interactions.

Email: yinglong.miao@gmail.com

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Continuum–based models for the description of mesoscale systems: from the molecular surface to chromatin compaction

Walter Rocchia[1]

1. CONCEPT Lab, Istituto Italiano Di Tecnologia, Via Morego 30, 16163 - Genova, Italy

The progress of powerful experimental techniques such as Cryo-Electron Microscopy represents a remarkable opportunity but also a significant challenge for computational techniques, which aim at extracting useful information and predicting the behavior of such systems. While pioneering attempts to perform molecular dynamics simulation at this scale by means of super-computers have been made, there still is the compelling need for enabling tools and approaches able to routinely analyze this kind of structures, identifying, for instance, interaction hot spots or new target regions for next generation drug discovery.
In this presentation I will describe the latest tool developments performed in my group in this direction, including the integration of NanoShaper, a tool for building and analyzing the molecular surface of systems at the nanoscale, with the widely used VMD software utility.
Among the others, the possibility of interfacing NanoShaper with the DelPhi Poisson-Boltzmann equation (PBE) solver allows remarkable accuracy and robustness in the calculation of the electrostatic energy of large systems.

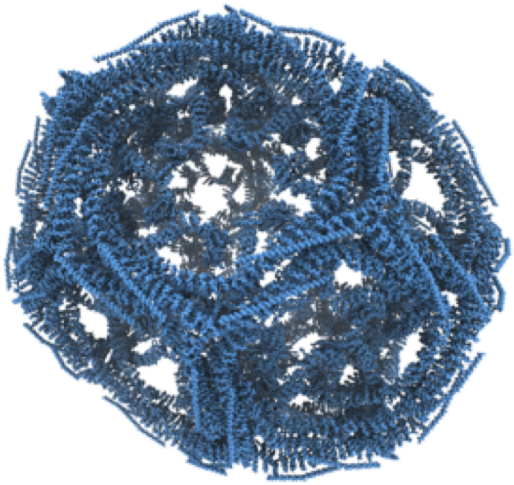

Figure 1. Solvent Excluded Surface of the clathrin coat protein built via NanoShaper and represented with VMD.

We are applying this computational toolkit to the derivation of constitutive parameters for a mesoscopic model of chromatin. In this model, we use the continuum media representation and the PBE formulation to derive energetic interaction terms between nucleosomes for which relates to electrostatics and solvation. We then derive parameters related to mechanical interactions between linked nucleosomes from full atom molecular dynamics. Put together, this is expected to provide a viable approach for the dynamical simulation of chromatin on the order of the Megabase size and beyond.

Email: walter.rocchia@iit.it

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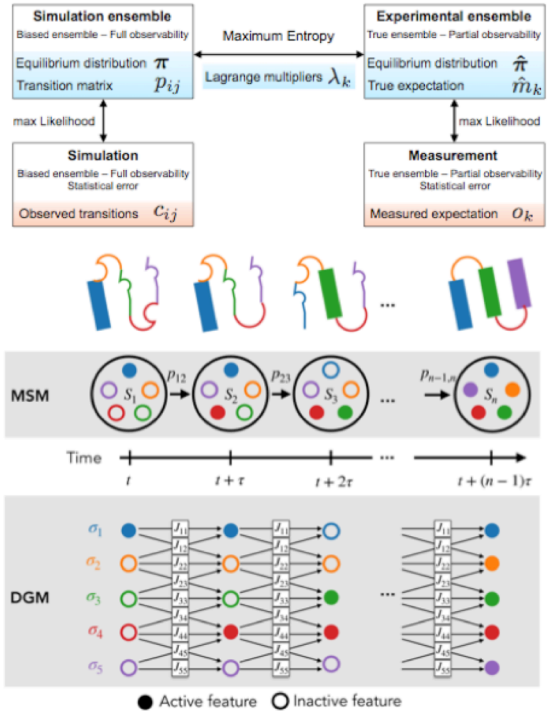
Addressing accuracy and size limitations in models of molecular kinetics

Simon Olsson[1]

1. Freie Universität Berlin



Experimental and computational methodology to characterize conformational distribution of biomolecular systems as 'thermodynamic ensembles' is becoming increasingly widely used. However, tackling the time-scales of conformational exchange between the major meta-stable configurations still constitutes a major obstacle to uncover molecular mechanisms in biological systems.

In the first part of this talk I will outline our recent method which allows integration of data from experiment and molecular dynamics simulations into atomistically resolved, kinetic models of conformational change. In doing this, we overcome both the partial observability of the experimental observables as well as the deficiencies in current molecular mechanics force fields. These models — Augmented Markov models — therefore constitute an important first step towards an integrative structural biology accommodating for kinetics of conformational change.

In the second part of this talk I will discuss issues arising for many current molecular modeling strategies for larger molecular subjects. Generally, the number of meta-stable configurations a molecule can adopt grows exponentially with the size of the molecule. In order to parameterize a model of these conformational changes we need to sample all the states, and all the possible interstate transitions. This quickly become intractable. To address this we have recently introduced Dynamic Graphical Models (DGM). By using local conformational sub-systems, DGMs side-step the necessity to sample all global molecular configurations and their interstate transition. Instead we only need to focus on sampling sub-system transition in the context of a local structural neighborhood. Effectively, these models are parametrically more compact, improving their statistical efficiency. In this manner DGMs may predict global molecular configurations which have not been explicitly observed during simulation. Indeed, we show DGMs may predict unobserved albeit physically realistic meta-stable configurations in proteins.

Email: solsson@zedat.fu-berlin.de

Lipid droplet budding: insight from molecular simulations

Monticelli, Luca,[1] Thiam, A. R.[1]

1. Molecular Microbiology and Structural Biochemistry (MMSB), UMR 5086 CNRS & Univ. Lyon, France
Laboratoire de Physique Statistique, ENS, Paris, France

Lipid droplets (LDs) are key cellular organelles regulating energy metabolism. LD biogenesis occurs in the ER membrane, by the demixing of synthesized neutral lipids into droplets, which then bud off from the ER. The fate and biological function of LDs are largely determined during their formation, but the driving forces and mechanism of LD formation remain elusive. Here, we use molecular dynamics simulations at the atomistic and coarse-grained level to gain insight into the driving forces for LD budding, and particularly the relationship between the shape of nascent LDs (that is a proxy for the tendency to bud off), its size, and its chemical composition. We also show that budding directionality can be determined simply by an asymmetry in bilayer surface coverage, with no requirement for specific membrane-bending proteins.

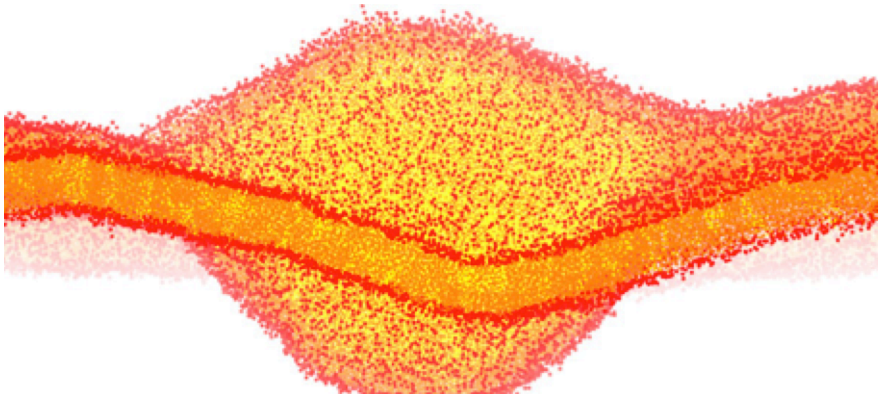


Figure 1. Side view of a lipid bilayer (18144 DOPC molecules, in orange; DOPC head groups are colored in red) with a nascent lipid droplet (7500 triolein molecules, in yellow). Water is not shown, for the sake of clarity. The lateral size of the system is about 78 nm. In the MARTINI coarse-grained description, the systems contains about 1.9M particles.

Email: luca.monticelli@inserm.fr

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Short-time diffusive dynamics of proteins in a naturally crowded environment

Hender Lopez

1. Institut Max von Laue - Paul Langevin (ILL), France. Institut für Angewandte Physik, Universität Tübingen, Germany. Université Grenoble Alpes, LiPhy, France

In living cells, 10-40 % of the intracellular fluid volume is occupied by macromolecules. This condition of macromolecular crowding influences reaction rates and signal transduction. We investigate the effect of crowding on the short-time tracer diffusion of model proteins on the nanometer length and sub-nanosecond timescales both experimentally and with the aid of computer simulations [1]. Experimentally, we dissolve polyclonal immunoglobulin (Ig) antibody proteins of natural isotopic abundance as tracers in perdeuterated Escherichia coli cell lysate as crowder to mimic a biological environment and at the same time optimize the sensitivity for the tracers using incoherent quasi-elastic neutron scattering. We subsequently compare the ensemble-averaged dynamics of Ig in lysate to the dynamics of Ig in pure water as a function of concentration. In both cases, remarkably, the diffusion of Ig only depends on the total macromolecular volume fraction φ in the sample, within the experimental accuracy (Fig. 1). To shed light on how polydispersity affects the short-time self-diffusion of proteins in crowded environments, we perform computer simulations which have proven to provide accurate information on the diffusion of proteins in crowed environments [2,3] and to interpret and rationalize neutron scattering experiments [4,5]. Because of the times scales and the relevance of hydrodynamic interactions (HI) in our experiments, we perform simulations based on Stokesian Dynamics [6] in which HI are considered explicitly and short-time properties can be calculated. In our approach, the lysate polydisperse system is modeled using hard spheres. We demonstrate an intricate dependency between the diffusion of a tracer on the crowder composition, specifically on the ensemble effective radius, Reff = (<Ri3>)1/3 (Fig. 1). For tracers with a radius close to Reff, the tracer diffusion is similar to that of a monodisperse system, whereas deviations are observed for significantly different tracer radii. Notably, the hydrodynamic radius of Ig is close to the lysate effective radius, which explains the surprising insensitivity to the polydispersity observed in the experiments. The simulation results further show that polydispersity slows down larger macromolecules more effectively than smaller ones even at nanosecond timescales. This has obvious implications for the functioning of the cellular machinery. Our simulations also confirm the predictive power, on the nanosecond timescale, of coarse-grained molecular dynamics simulations.

Email: hender.lopezsilva@ucd.ie

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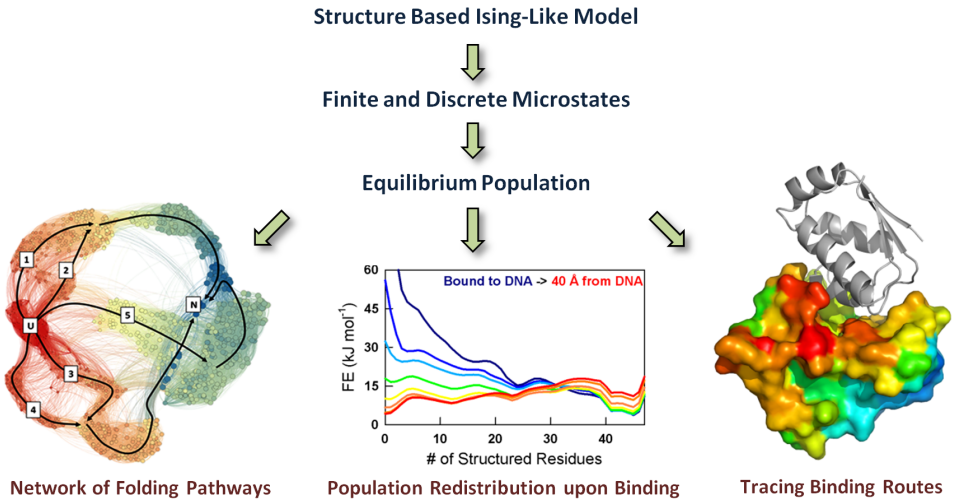
Simulation of Long Time-Scale Events by Phase Space Reduction

Soundhararajan Gopi[1], Sayan Ranu[2] and Athi N. Naganathan[1]

1. Indian Institute of Technology Madras, Chennai 600036, India.
2. Indian Institute of Technology Delhi, New Delhi 110016, India.

Elucidating protein folding and binding landscapes through computational methods in an experimentally-consistent manner is limited primarily by conformational sampling and force-field deficiencies. Recent advances like machine intensive molecular dynamics (MD) simulations and Markov state models provide avenues to overcome these bottlenecks. Here we showcase a novel residue-level treatment of folding-binding phenomena that is highly scalable combining concepts from statistical mechanics, physical kinetics and graph theory. The simplified phase space description and experimentally derived energy-entropy function in this Ising-like model dramatically improves the sampling efficiency allowing us to simulate >10000 (un)folding events, for multiple proteins and thermodynamic conditions. We show that this treatment provides an unprecedented insight into folding pathway heterogeneity in proteins and their molecular origins. In parallel, it is possible to identify and describe even protein-DNA binding mechanisms using a similar approach. We present a case study on an intrinsically disordered DNA binding protein (CytR) that is shown to electrostatically pre-organize itself in a distance dependent manner contributing to a novel 'continuous conformational selection' mechanism of binding. We extend the same approach to protein-protein binding using Barnase-Barstar complex as a test case. We identify binding routes, intermediate and meta-stable states contributing to the native complex in very good agreement with recent all-atom MD simulations. Importantly, the model generates free energy profiles for different binding poses and at different distances between the two molecular partners (20000-82000 and ~120000 poses and hence the free energy profiles in CytR-DNA and Barnase-Barstar complexes, respectively) in a rapid manner providing a unique view of folding-binding phenomena. Further improvements to our model and sampling methodology can open up ways to explore general trends in folding-binding processes of not just large macromolecular complexes but also disordered proteins.

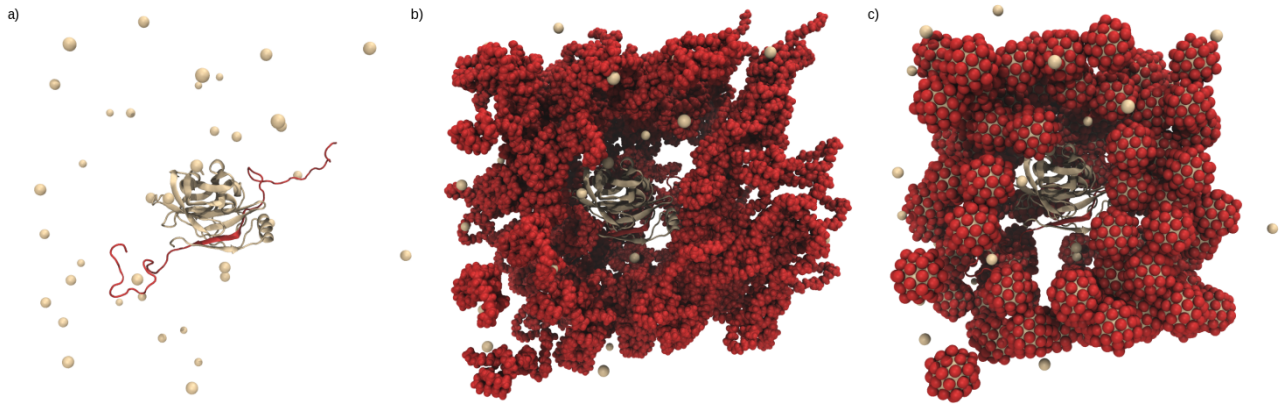


Email: soundharar@gmail.com

Effect of crowding on the dynamics of the hepatitis C virus protease NS3/4a

Natalia Ostrowska,[1,2] Michael Feig,[3] Joanna Trylska[1]

1. Centre of New Technologies, University of Warsaw, Warsaw, Poland
2. College of Inter-Faculty Individual Studies in Mathematics and Natural Sciences, Warsaw, Poland
3. Department of Biochemistry and Molecular Biology, Michigan State University, United States



The aim of our work is to determine how the crowded environment affects the dynamics of one of the hepatitis C virus (HCV) proteases – NS3/4a – and the diffusion of its ligands toward the active site. Crowding may affect enzyme conformational dynamics, which can further affect the formation of the enzyme-substrate or enzyme-inhibitor complexes, diffusion of the substrates toward the active site and enzymatic reaction rates. Therefore, investigating enzyme dynamics and interactions in crowded solutions is crucial for understanding their function. By performing molecular dynamics simulations, we investigate the effects of crowding on the HCV NS3/4a protease internal dynamics. The NS3/4a protease from the HCV virus plays a key role in viral replication and has been successfully used as a target for anti-viral treatment. The NS3 protein forms a stable heterodimer with its disordered peptide cofactor NS4a.

In our simulations the enzyme and water molecules are described at atomistic resolution and crowders via either all-atom or coarse-grained models. Crowders reflect the polyethylene glycol (PEG) molecules used in the experiments to mimic the crowded surrounding. The folded PEG molecule in a coarse-grained model is represented as a sphere of spheres. It resembles a hydrophilic character of the PEG, shows minimal interactions with the protein and provides mainly the excluded volume effect. Simulations in the presence of crowders surrounding the enzyme are compared with the enzyme alone, with particular emphasis on the NS4a cofactor's mobility.

Our research provides insight into the behaviour of the proteins under crowded conditions and could help design better anti-HCV treatment. Furthermore, we designed coarse-grained crowders that can be used in all-atom simulations and speed them up by 20%.

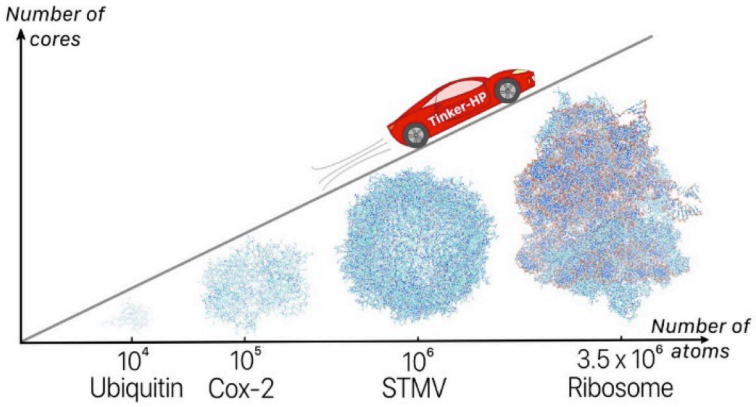
Email: n.ostrowska@cent.uw.edu.pl

Scalable polarizable molecular dynamics using Tinker-HP: millions of atoms on thousands of cores

Jean-Philip Piquemal[1-3]

1. Sorbonne Université, 75005, Paris, France.
2. Institut Universitaire de France, 75005, Paris, France.
3. Department of Biomedical Engineering, the University of Texas at Austin, TX, USA.

Tinker-HP (http:///www.ip2ct.upmc.fr/tinkerHP) is a CPU based, double precision, massively parallel package dedicated to long polarizable molecular dynamics simulations and to polarizable QM/MM. Tinker-HP is an evolution of the popular Tinker package (http://dasher.wustl.edu/tinker) that conserves it simplicity of use but brings new capabilities allowing performing very long molecular dynamics simulations on modern supercomputers that use thousands of cores. The Tinker-HP approach offers various strategies using domain decomposition techniques for periodic boundary conditions in the framework of the (N)log(N) Smooth Particle Mesh Ewald. Tinker-HP proposes a high performance scalable computing environment for polarizable force fields giving access to large systems up to millions of atoms. I will present the performances and scalability of the software in the context of the AMOEBA force field. Various benchmarks and examples on biomolecular systems will be provided on several architectures. As the present implementation is clearly devoted to petascale applications, the applicability of such an approach to future exascale machines will be exposed and future directions of Tinker-HP discussed in the framework of our ERC SYG EMC2 project.



Email: jpp@lct.jussieu.fr

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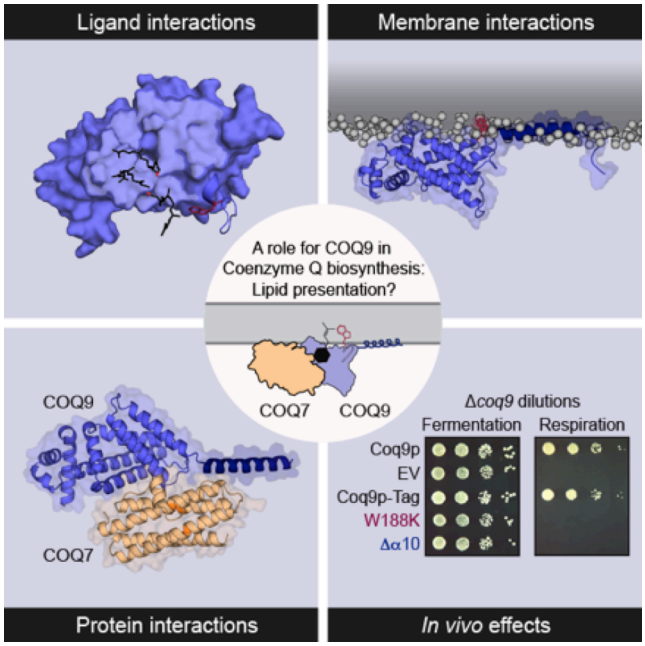
Overcoming the hydrophobic barrier of the membrane: The role of COQ9 in promoting coenzyme Q biosynthesis

Deniz Aydin[1], Danielle C. Lohman[2], David J. Pagliarini[2], Matteo Dal Peraro[1]

1. Institute of Bioengineering, School of Life Sciences, Swiss Federal Institute of Technology (EPFL), and the Swiss Institute of Bioinformatics (SIB), 1015 Lausanne, Switzerland
2. Department of Biochemistry, University of Wisconsin-Madison, and Morgridge Institute for Research, Madison, WI 53706, USA



Integral and peripheral membrane proteins account for one-third of the human proteome, and they are estimated to represent the target for over 50% of modern medicinal drugs. Despite their central role in medicine, the complex, heterogeneous and dynamic nature of biological membranes complicates the investigation of their mechanism of action by both experimental and computational techniques. Among the different membrane bound compartments in eukaryotic cells, mitochondria are highly complex in form and function, and they harbor a unique proteome that remains largely unexplored. A growing number of inherited metabolic diseases are associated with mitochondrial dysfunction, which necessitates the structural and functional elucidation of mitochondrial proteins. In this work, we explore the lipid binding activity of COQ9, a member of the mitochondrial coenzyme Q biosynthesis machinery that is structurally characterized but remains functionally obscure [1]. We reveal that COQ9 repurposes an ancient bacterial fold to selectively bind aromatic isoprenes, including CoQ intermediates that reside within the bilayer. Through molecular simulations, we elucidate the mechanistic details of its membrane binding process, by which COQ9 warps the membrane surface and creates a tightly sealed hydrophobic region to access its lipid cargo. Finally, we establish a potential molecular interface between COQ9 and COQ7, the enzyme that catalyzes the penultimate step in CoQ biosynthesis, suggesting a model whereby COQ9 presents intermediates to CoQ enzymes to overcome the hydrophobic barrier of the membrane. Collectively, our results provide a mechanism for how a lipid binding protein might access, select, and extract specific cargo from a membrane and present it to a peripheral membrane enzyme. We anticipate our integrative methodologies and mechanistic findings will prove relevant to other lipid binding proteins, whose fine functional modulation at the membrane-water interface has been historically challenging to characterize.

Email: d.aydin@epfl.ch

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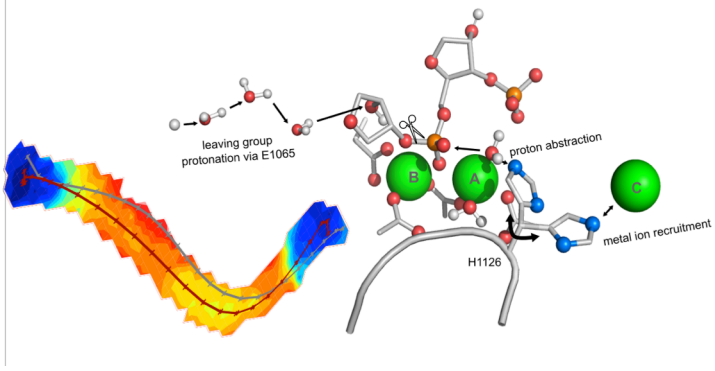
5 Posters

The dual role of histidine as general base and recruiter of a third metal ion in HIV-1 RNase H

Simon L. Dürr[1,2], Olga Bohuszewicz[1], Reynier Suardiaz[1], Pablo G. Jambrina[1], Christine Peter[2], Yihan Shao[3], Edina Rosta[1]

1. Department of Chemistry, King's College London, London, SE1 1DB, United Kingdom
2. Department of Chemistry, Uni- versity of Konstanz, 78457 Konstanz, Germany
3. Department of Chemistry and Biochemistry, University of Oklahoma, Nor- man, Oklahoma 73019, USA



RNase H is a prototypical example for two metal ion catalysis in enzymes. An RNase H activity is present in the HIV-1 reverse transcriptase but also in many other nucleases such as Homo sapiens (Hs) or Esche- richia coli (Ec) RNase H. The mechanism of the reaction has already been extensively studied based on the Bacillus halodurans (Bh) RNase H crystal structure1–3 most recently using time-resolved X-Ray crys- tallography. However, kinetic and mutation experiments with HIV-1, Hs and Ec RNase H implicate a catalytic histidine in the reaction not present in Bh RNase H and the protonation of the leaving group also remains poorly understood.4

We use quantum mechanics/molecular mechanics (QM/MM) calculations combining Hamiltonian rep- lica exchange with a finite-temperature string method to study the cleavage of the ribonucleic acid (RNA) backbone of a DNA/RNA hybrid catalyzed by the HIV-1 RNase H with focus on the proton transfer pathway and the role of the histidine. The reported pathway is consistent with kinetic data obtained with mutant HIV-1, Hs and Ec RNase H, the calculated pKa values of the DEDD residues and crystallographic studies. The overall reaction barrier of ~16 kcal mol -1, encountered in the first step, matches the slow experimental rate of ~1-100 min-1.

Using Molecular dynamics (MD) calculations we are able to sample the recently identified 3 binding site for a third transient divalent metal ion in the vicinity of the scissile phosphate in the product complex. Based on data from our simulations, a similar observation of a third metal ion facilitating product release in an Aquifex aeolicus RNase III crystal structure5 and the in crystallo reaction3 we are able to show that the third ion and the histidine are key to product release as had been hypothesized.4

Email: simon.durr@epfl.ch

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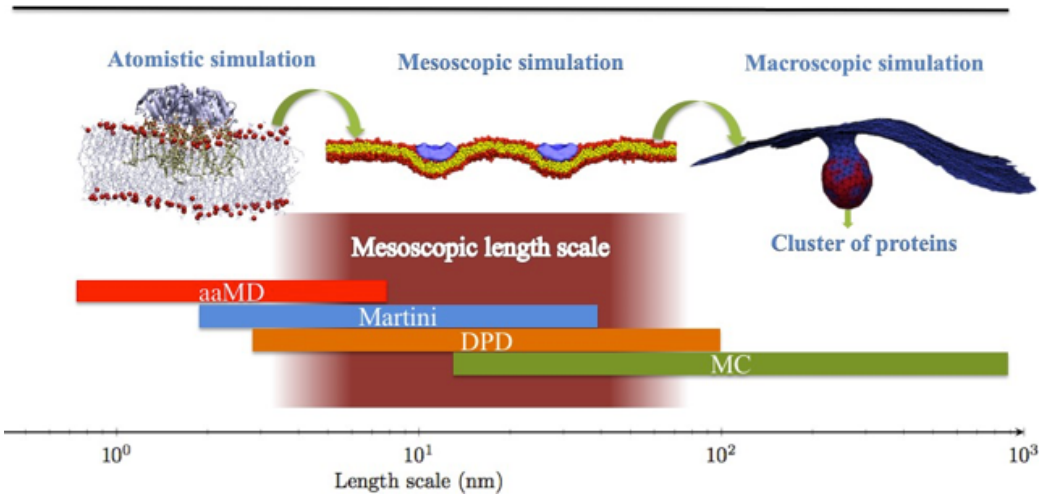
Shape transformations of biological membranes, from atomistic to macroscopic length scale: Perspective for building a synthetic cell.

Weria Pezeshkian,[1] John H. Ipsen,[2] Julian Shillcock,[3] Siewert-Jan Marrink[1]

1. Faculty of Science and Engineering, Molecular Dynamics, Groningen University, Groningen, Netherlands.
2. Center for Biomembrane Physics (MEMPHYS), University of Southern Denmark, Odense , Denmark.
3. Ecole Polytechnique Federale de Lausanne (EPFL), 1015 Lausanne, Switzerland.

The large scale conformational properties of the membrane are governed by its curvature elastic energy and the lateral organization of the membrane and membrane-proteins, and only a few model parameters are involved. Although the membrane curvature elastic energy is well described by Helfrich Hamiltonian, modelling the lateral organization of its constituents requires a calibration form lower length-scales.We are using distinct computer simulation techniques from atomistic (all-atom molecular dynamics) to mesoscopic length scales (Martini model and Dissipative particle dynamics) to feed our Monte Carlo simulations of fluid triangulated surfaces that can describe large scale membrane shape conformations. We have applied this technique and properly described the formation of membrane invaginations upon binding nanoparticles and membrane proteins.

For the theoretical phase of a new research program, BaSyC-Building a Synthetic Cell, to create an autonomous and self-reproducing synthetic cell, we are going to use this multi-scale simulation approach to decipher conditions of spontaneous membrane fission. Our aim is to find a minimal system, in which a vesicle spontaneously transform into a dumbbell-like shape. Then, an active process can split this structure into two vesicles, reminiscent of the cell division.



Email: weria.pezeshkian@gmail.com

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DNA-Protein interactions rule in the DNA binding specificity of Androgen and Glucocorticoid receptors

Mahdi Bagherpoor Helabad[1], Senta Volkenandt[1] , Petra Imhof[1]

1. Physics Department, Freie Universität Berlin, Berlin, Germany

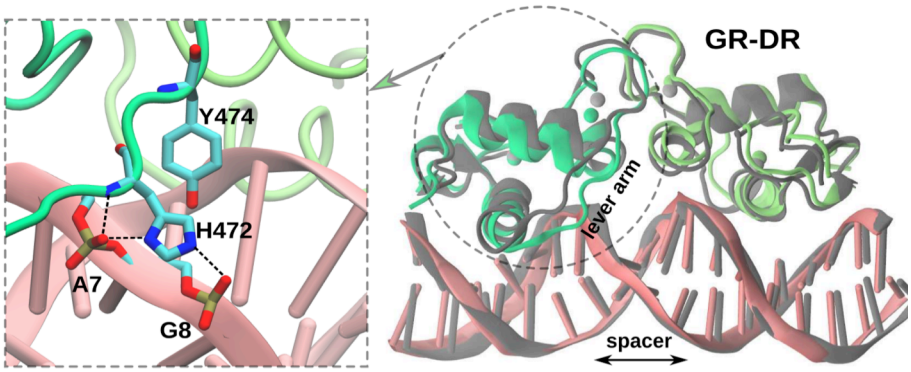

Figure 1. Conformational change of the lever arm, and therefore strong hydrogen bond of residue H472 with spacer, leads an unstable conformation in the GR-DR.

Transcription factors (TFs) are essential in gene regulation process. Glucocorticoid (GR) and Androgen (AR) receptors are ligand-activated TFs that can bind as a homodimer to specific target DNA, which resembles an inverted repeat (IR) of a hexamer ”AGAACA” separated with three base pairs called spacer [1]. Direct repeat (DR) of this hexamer solely can be recognized by the AR. The question why despite the similar structure of GR DNA binding domain (DBD) to AR, it is not able to reach a stable bound state with DR-like elements is still a matter of debate [2,3]. In this study, by employing the all-atom MD simulation, we aim to address the factors that govern the preferential DNA recognition of the AR/GR DBD bound state. Our result demonstrates that conformation of monomer A of the GR-DR complex, which is interacting with first DNA half-site, is significantly changed during the simulation. In fact, we show that strong hydrogen bond interactions of the residue H472 (in the lever arm region of DBD) with the spacer, which is facilitated by a conformational change of the adjacent lever arm residues, can be a key factor in destabilizing of the GR-DR complex, see Figure 1. This idea is fully supported by our mutation study. The mutation of residue, i.e. H472R, in both GR-IR and GR-DR complexes importantly changes the dimerisation interface of the monomers, in agreement with experimental studies [4]. Interestingly, in the GR(H472R)-DR system, conformation of the monomer A, and therefore lever arm residues, changes quite similar to those of conformational changes that we have observed in GR-DR system. Therefore, a hydrogen bond interaction of R472 (in GR(H472R)-DR) with the spacer, as we observed for H472 in wild-type GR-DR, significantly destabilize the interaction of the GR in complex with DR. Furthermore, we demonstrate that the AR-DBDs dimer interface, as well as the AR-DBDs-/DNA interactions, vary, depending on the bound response elements. Analysis of the communication network available within and between different domains of the protein-DNA complexes shows that the communication between two half-sites is not only connected via the monomers dimerisation region but also via the protein-DNA interface. Furthermore, we show that the lever arm-spacer interface plays a predominant role in this allosteric communication between the dimerisation domain and the protein monomers with their respective DNA hexamers, thus controlling stable complex formation.

Email: mbagerpoor@zedat.fu-berlin.de

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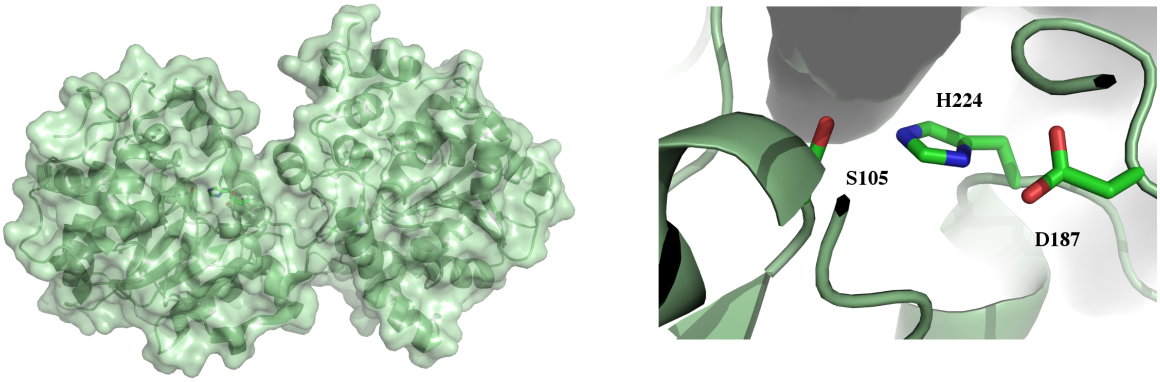
Catalytic cycle of CALB towards the synthesis of poly(ε-caprolactone)

Pedro Figueiredo,[1] Alexandra Teresa Pires Carvalho[1]

1. Center for Neuroscience and Cell Biology, Institute for Interdisciplinary Research (IIIUC), University of Coimbra



Bio-based polymers have gained much attention in the biomedical feld, especially in tissue engineering [1] but also as drug delivery systems [2,3], since these materials are non-toxic, biodegradable and bio-compatible [1]. Poly(ε-caprolactone) is one of these bio-based polymers that have been used in a wide range of scafold fabrication technologies [3].
Enzymes can be employed in the synthesis of these materials, particularly lipases. Lipases are hydrolases for the carboxyl ester bond of hydrophobic substrates, namely triacylglycerols, phospholipids and other insoluble substrates, acting in aqueous reacting medium as well as in low-water medium, possessing considerable physiological signifcance with high interest also for their industrial applications [4]. Candida Antarctica Lipase B (CALB) efciently catalyzes the ring-opening polymerization (ROP) of ε-caprolactone to products with medium molecular weight [5]. In this work we investigated the full catalytic cycle for ring- opening polymerization of ε-caprolactone in water and toluene medium using quantum mechanical/molecular mechanical (QM/MM) calculations [6].

Email: pmrfigueiredo@cnc.uc.pt

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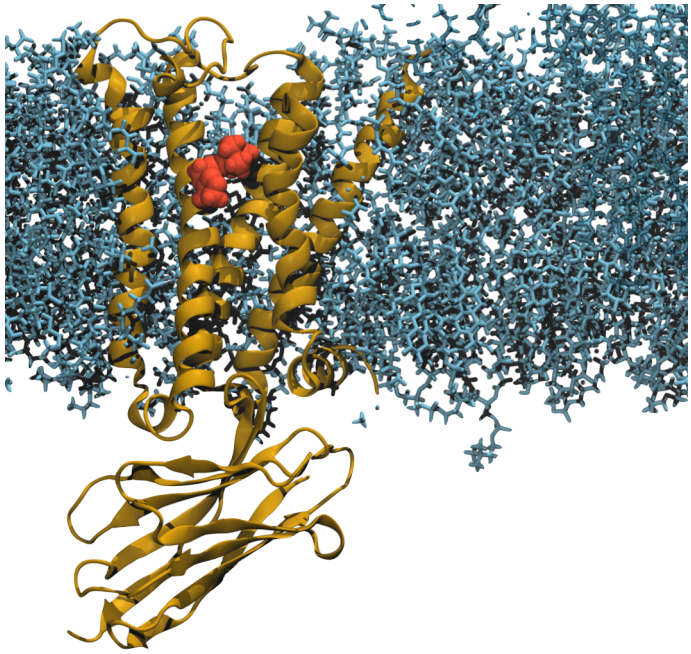
Uncovering molecular recognition of a ligand binding to the M2 muscarinic receptor

Riccardo Capelli[1], Anna Bochicchio[1], GiovanniMaria Piccini[2], Rodrigo Casasnovas[1], Paolo Carloni[1,3], Michele Parrinello[2,4].

1. Computational Nanomedicine (INM-9/IAS-5), Forschungszentrum Juelich, Juelich, Germany
2. Department of Chemistry and Applied Biosciences, ETH Zürich, and Istituto di Scienze Computazionali, USI, Lugano, Ticino, Switzerland
3. Department of Physics, RWTH Aachen University, D-52078 Aachen, Germany
4. Istituto Italiano di Tecnologia, Genova, Italy



Predicting the complete free energy landscape associated with protein-ligand unbinding would greatly help design drug leads with highly optimized pharmacokinetics. To this effect we use funnel metadynamics [1], an enhanced sampling method especially designed for the study of ligand (un)binding. The efficiency of metadynamics like that of other sampling methods depends critically on the identification of collective variables able to discriminate the slow degrees of freedom of the system. In order to identify such collective variables we combine two methods, Ratchet&Pawl MD [2] and Harmonic Linear Discriminant Analysis (HLDA) [3]. In this way, we show that one can identify the few essential reaction coordinates of the process. We apply this to the iperoxo agonist to its target human neuroreceptor M2, embedded in a neuronal membrane. This computationally affordable protocol is totally general and it can be applied in a straightforward manner to determine the full free energy landscape in other membrane receptors/drug unbinding processes.

Email: riccardo.capelli@icrm.cnr.it

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A Combined Molecular Dynamics-Variational Multi-Scale Method to Explore the Transition Paths between Proteins States

Francesco Delfino[1,2], Yuri Porozov[1,3], Eugene Stepanov[3,4], Gaik Tamazian[5], Valentina Tozzini[2].

1. I.M. Sechenov First Moscow State Medical University, Trubetskaya st. 8-2, Moscow 119991, RUS
2. Istituto Nanoscienze CNR & NEST-Scuola Normale Superiore, Piazza San Silvestro 12, 56127 Pisa, IT
3. ITMO University, 49 Kronverksky Av., St. Petersburg 197101, Russia
4. St Petersburg Branch of the Steklov Mathematical Institute of the Russian Academy of Sciences, Fontanka 27, 191023 St Petersburg, RUS
5. Department of Mathematical Physics, Faculty of Mathematics and Mechanics, St Petersburg State University, Universitetskij pr. 28, Old Peterhof, 198504 St Petersburg, RUS

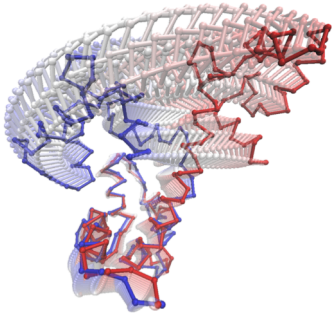

Figure 1. Calmodulin transition from closed (1WRZ) to open (1EXR) structure, obtained with the PROMPT method.

Signaling is a core activity in cells. Most of the signaling processes are regulated by bi- (or multi-) stable proteins, which can undergo conformational changes in response to changes in environmental conditions or stimuli of different origin.[1] The structural variations are usually quite large, therefore atomistic molecular dynamics (MD) simulations might not be the most proper method to address them, both because the slow transition kinetics requires simulations exceeding the currently reachable time and space scales, and because standard empirical atomistic force fields start to reveal their deficiencies, especially with the strongly distorted transition states.[2] Strategies to overcome these difficulties involve different actions. On one side, adopting simplified low-resolution descriptions of the system such as coarse-grained models[3] reduces the computational cost and allows performing a more efficient sampling of the conformational space. On the other side, one can act by simplifying the sampling algorithm. The morphing-related methods connect the starting and final states based on some optimization strategy.[4-7] In particular PROMPT[8,9] employs an approach based on the optimal mass transportation problem including physical constraints of geometric nature,[10] without relying on any specific force field. The MinActionPath (MAP) method[11] reintroduces some physical interaction in the system and finds the optimal path by minimizing the action integral. The aim of this work is to set up and validate a modeling strategy based on the comparison and mixing of the several described methods to find the optimal transition paths between given states. We illustrate and apply our strategy to a set of bi-stable proteins chosen for their bio-chemical relevance, highlighting the advantages and the limitations, and discussing them on a physical-chemical background. The figure illustrates the transition path obtained with the PROMPT method for Calmodulin, a Ca-binding protein involved in the calcium signal transduction pathway.

Email: delfinofrancesco90@gmail.com

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Dynamic pH in coarse-grained MARTINI simulations

Fabian Grunewald*[1], Paulo C. Telles de Souza[1], Haleh Abdizadeh[1] and Siewert J. Marrink**[1]

1. Groningen Biomolecular Sciences and Biotechnology Institute and Zernike Institute for Advanced Materials, University of Groningen, Groningen, The Netherlands

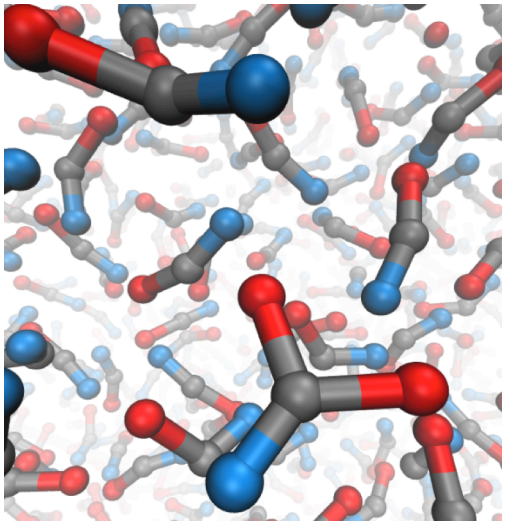

Figure 1. Protonated MARTINI water particle in bulk of polarizable MARTINI water; the blue/red spheres represent the offset charges used for generating polarizability and the gray spheres represent the vdw-interaction center. The red spheres can detach and attach to the LJ interaction center to mimic protonation.

Over the past two decades coarse-grained molecular dynamics methods have been developed that routinely reach length scales of several hundred nanometers and time scales in the order of microseconds. One of these approaches is the MARTINI force-field (Marrink et al. 2007). In the MARTINI force-field about four heavy atoms are grouped into one interaction center, called bead. The interactions between beads represent the nature of the underlying chemical groups; the strength of the interaction is selected from a discrete set of levels by reproducing the free energies of transfer. Using this approach a wide variety of biological and other chemical systems have been successfully simulated. Here we present the current state of the extension of the MARTINI model to constant pH simulations. Our approach uses empirical classical potentials and is based upon the polarizable MARTINI water model. The polarizable MARTINI water represents 4 water molecules as one bead. It includes two charges, which are off-set from the center of the Lennard-Jones (LJ) interaction (Yesylevskyy et al. 2010 and Michalowsky et al. 2017). The two offset charges reproduce the polarizability and dielectric screening of water. Protonation in our model is mimicked by transfer of a positive particle to a protonizable bead. The particle transfer implicitly changes the type of the protonizable bead by changing the total charge and LJ interactions of that bead. Note that this particle should not be viewed as an explicit proton but rather a pseudo particle carrying the difference in interactions between a neutral and protonated bead. Interactions of the protonizable beads with all other particles are derived from reproducing the partition free energies at pH-values such that the protonizable bead is neutral. Contrary to lambda dynamics within MARTINI (Bennett et al. 2013) the total charge is conserved. Additionally this approach is potentially extendable to multiple other reactions. Using explicit particles to reproduce changes in interaction levels between beads - that is reactions - also opens the route to out of equilibrium dynamics.

Email: f.grunewald@rug.nl

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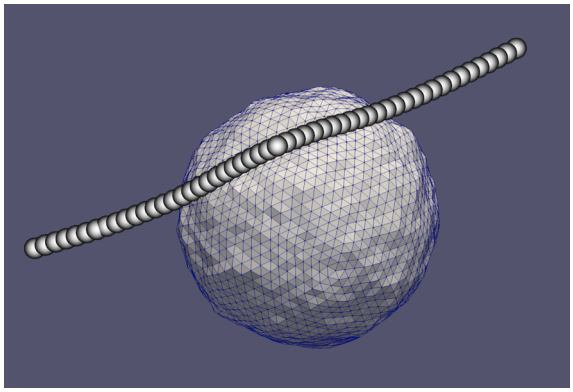
Peptide nanofibrils as enhancers of viral infection

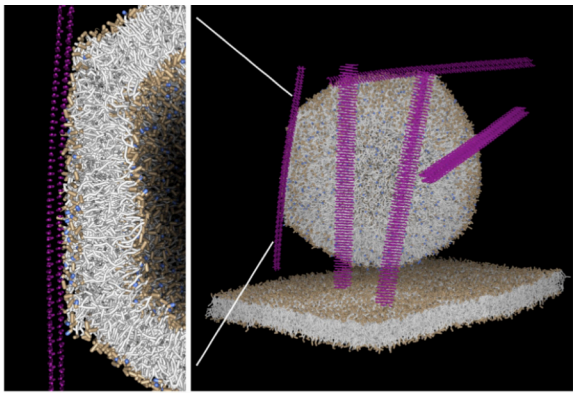
Kai Steffen Stroh[1] and Herre Jelger Risselada[1,2]

1. Institute for Theoretical Physics, Georg-August-University Göttingen
2. Leiden Institute of Chemistry, Leiden University

It has been shown experimentally that amyloid fibrils, which are naturally present in seminal fluid, may increase the infectious viral titer of HIV-1 by four to five orders of magnitude [1]. These fibrils termed SEVI (semen-derived enhancer of viral infection) interact with HIV-1 virions and promote their attachment to target cells, resulting in accelerated fusion. While the inhibition of this process would be of interest in the context of HIV, fusion enhancement is desirable for targeted retroviral gene transfer and drug delivery. The mechanism of infection enhancement is not yet fully understood. While the positive surface charge of the amyloid fibrils evidently plays a role in bringing the negatively charged viruses and cells in contact [2], the increased infectivity also appears to depend on the intrinsic properties of the fibril structures [3], such as fibril stiffness and fibril length. To reconstruct the interaction landscape that amyloid fibril covered viruses face when undergoing fusion with a host cell, we employ elastic continuum models in conjunction with coarse grained molecular dynamics simulations.



(a) Virion and fibril in continuum model



(b) MD simulation of virion, fibrils and host cell

Email: kai.stroh@theorie.physik.uni-goettingen.de

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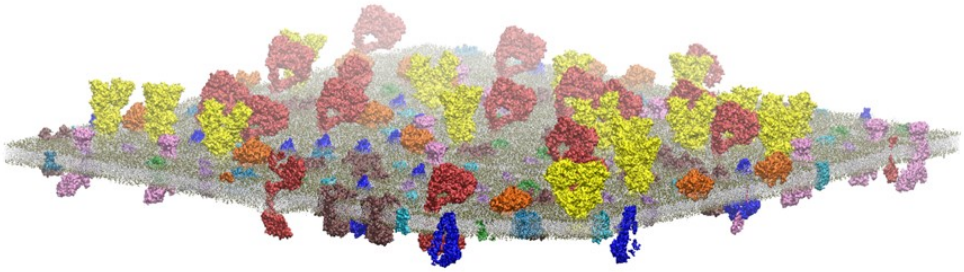
A molecular view of crowded and complex membranes

Haleh Abdizadeh[1], M. Koning[1], A. Mazumdar[1], S.J. Marrink[1]

1. Groningen Biomolecular Sciences and Biotechnology Institute and Zernike Institute for Advanced Materials, University of Groningen, Groningen, The Netherlands



Cellular membranes are asymmetric mixtures of lipids and membrane proteins that separate the cell interior from the outside environment.1 Plasma membranes have hundreds of lipid species whose actual composition is regulated by the cell and varies between organelles and organisms.2 The question then arises as to the structural heterogeneity and lateral organization of lipids around the membrane proteins. This is a challenging problem as malfunctioning at the level of lipid-protein interaction and bilayer properties in the crowded cellular membranes are implicated in numerous diseases.3 Thus, in-silico modeling of prototypical crowded membranes provides insight into the detailed microscopic understanding of the large-scale cell membrane behavior. We have used coarse-grained molecular dynamics simulations to study the lipid environment of 10 different proteins in a prototypical plasma membrane of 60 lipid species in a membrane patch of 150 nm x 150 nm. To provide a view of overall organization of lipid environments in cells, our analyses focus on characterizing the specific and non-specific lipid interactions with different proteins, impact of lipid composition on protein-protein interactions, protein cluster formation as mediated by lipids, and diffusion of various species of the system under the crowded condition.

Email: h.abdizadeh@rug.nl

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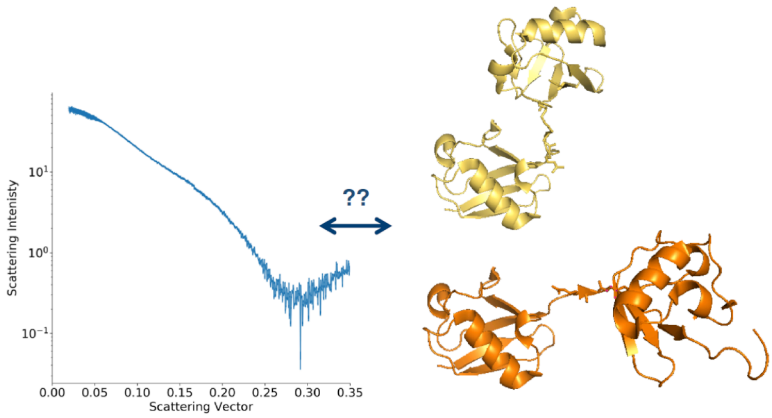
MD simulations driven by saxs experimental data

Cristina Paissoni[1], Alexander Jussupow[2] & Carlo Camilloni[1]

1. University of Milan, Biosciences Department, Via Celoria 26, 20133 Milan (Italy)
2 Technische Universitat Munchen, Department of Chemistry and Institute for Advanced Study, Lichtenbergstr. 4, 85747 Garching (Germany)

Small-angle X-ray scattering (SAXS) experiments are well-suited methods to characterize biomolecules in solution. Nevertheless, its low information content hinders a straightforward determination of conformational ensembles, leading to the risk of overfitting. To overcome this issue, a strategy consists in complementing experimental information with accurate physical models, as the one that are provided by molecular mechanic force fields. However, several challenges must be faced. Firstly, it must be considered that experimental data are often provided as ensemble-averages and are subjected to random and systematic errors. Further, from a computational perspective, calculating scattering profiles given a structure of N atoms is extremely demanding as it is an O(N2) problem.



Here we present a method, based on Metainference, that aims to overcome the difficulties previously listed integrating SAXS data as restraints in MD simulations. This approach follows the idea of the replica-averaging modelling to account for conformational averaging in SAXS and exploits Bayesian inference to deal with both random and systematic errors. The problem of the high computational cost in the computation of scattering intensities is faced adopting a hybrid coarse-grained/all-atom approach, where the simulations are run with full atomistic details, while a coarse-grained representation of the 3d-structures, based on the Martini forcefield, is used to allow a faster back-calculation of SAXS intensities. To this aim we exploited the recently developed Martini form factors for protein beads that we extended also to nucleic acids.

Three test cases are presented. Two protein/nucleic-acid complexes have been refined against SAXS data with our approach. Further, we have studied the conformational space of K63-linked diubiquitin, which is known to populate highly different conformational states. SAXS data were used to restrain the simulations, while additional NMR-derived experimental information were exploited to confirm the reliability of the reconstructed models.

Overall, the method proposed is expected to provide a solid basis for the integration of SAXS data in MD simulations, allowing the accurate determination of biomolecular structural ensembles, also in the cases of highly heterogeneous systems. Notably, thanks to the flexibility of the Metainference approach, this technique could be easily extended to include experimental data coming from different sources.

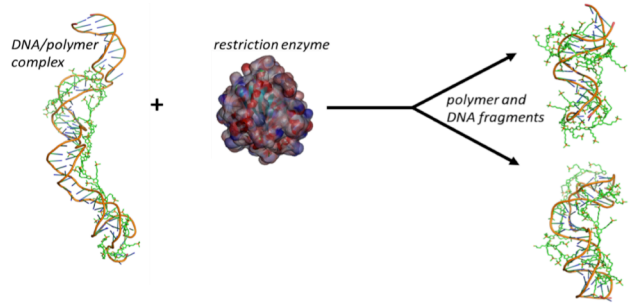
Email: cristina.paissoni@gmail.com

Dynamics and induced chirality in the self-assembly of DNA with a π-conjugated polymer

Mathieu Fosséprè[1], Marie E. Trévisan[1], Jenifer Rubio-Magnieto[1], David Beljonne[1], Mathieu Surin[1]

1. Laboratory for Chemistry of Novel Materials, Center for Innovation in Materials and Polymers, University of Mons - UMONS, 20 Place du Parc, B-7000 Mons, Belgium

DNA-templated self-assembly is of great interest for directing the organization of functional molecules and for potential applications in DNA sensing.1-2 The richness of interactions in DNA were often exploited for organizing π-conjugated (macro)molecules into large supramolecular structures.1-4 Computational molecular modelling approaches, such as Molecular Dynamics (MD), play an increasingly important role for studying the structure, dynamics, and function of biomolecular systems and to complement experimental results.5 Molecular modelling of DNA has progressed a lot in the last decade, several spatial-resolution models of DNA are now available, from all-atom representation to highly coarse-grained DNA models, or even hybrid resolution models.6 Although the high computational cost of the all-atom approach restricts the length and time scales that can be considered, it is still the most appropriate strategy to study precisely the inner structure of DNA. All-atom MD simulations are becoming a routine technique to bring molecular insights into the interactions at play, the structure and the dynamics of DNA-templated supramolecular complexes.



In this context, we performed MD simulations to study the self-assembly of DNA with an achiral cationic polythiophene, a π-conjugated polyelectrolyte increasingly considered for optical biosensing.4,7 We show that DNA/polymer self-assembly can present different level flexibility according to the length of DNA fragments. We illustrate how the polymer organization along the DNA duplex is promoted, reporting various types of global shapes and geometries of the DNA/polymer assemblies. We discuss how the induced chirality from DNA to the polymer emerges through different spatial scales. In particular, the influence of the size of DNA fragments on the conformational chirality of the polymer is investigated thanks to the numerous polymer conformations issued from our MD simulations. For this, continuous symmetry measurements as well as quantum-chemical calculations are employed to quantify the symmetry and the chirality of the polymer conformations,8 in relationship with chiroptical measurements.

Email: mathieu.fossepre@umons.ac.be

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Force-mediated modulation of the pharmacological response of receptor tyrosine kinases

Francesco Aquilante[1], Zuleika Calderin-Sollet[2], Seimia Chebbi[2] & Bernhard Wehrle-Haller[2]

1. University of Geneva, Department of Physical Chemistry, Geneva, Switzerland
2 University of Geneva, Centre Médical Universitaire, Geneva, Switzerland

A pivotal problem of molecular dynamics (MD) applied to the study of biological processes is the necessity to span time scales sufficient to cover the unbinding of ligands and conformational changes in biomolecules. Due to the roughness of the prototypical energy landscapes, standard MD simulations can be extremely inefficient at this task, but a viable alternative is represented by the introduction of a biasing potential that flattens the energy landscape. [1] Here we have attempted to use this technique for an in silico identification of new classes of tyrosine kinase inhibitors (TKI's) that can eliminate cancer cells in their niches. At the most fundamental level, this work aims at understanding the force-mediated conformational changes in the c-Kit tyrosine kinase domain. Kit Ligand (KitL) and its receptor c-Kit are critical for germ cells, melanocytes, hematopoietic stem cells and mastocytes. C-Kit kinase activating mutations can cause various forms of cancer, including leukemia. Despite treatments with TKIs, notably imatinib, tumor cells persists in the tissue microenvironment of the bone marrow, which can cause the development of TKI-resistant mutations in c-Kit and tumor relapse. So far, it is not understood why tumor cells are sensitive to TKI inhibitors when present in the blood, but escape this treatment when anchored to their niche in the bone marrow. An experimental system has been built in our group [2] in order to analyse the pharmacological response of wildtype or oncogenic c-Kit receptors, when anchored to surface-immobilized KitL. Results from these experimental investigations show for example that c-Kit kinase activation and downstream signalling in response to immobilized-KitL is no longer inhibited by imatinib, which blocks however signalling by soluble ligand and which binds to the inactive conformation of the kinase. Further insights on the understanding of such behavior, as well as on a number of additional experimental findings have come from the use of MD simulations as presented in this work.

Email: francesco.aquilante@gmail.com

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Unveiling the role of ether lipids in Golgi-ER retrograde transport

Valeria Zoni[1], Noemi Jiménez-Rojo[2], Manuel Leonetti[3], Adai Colom[2], Dimitri Moreau[2], Suihan Feng[2], Isabelle Riezman[2], Aurélien Roux[2], Jonathan Weissman[3], Howard Riezman[2], Stefano Vanni[1]

1. Department of Biology, University of Fribourg, Switzerland
2. Department of Biochemistry, University of Geneva, Switzerland
3. UCSF, California, US.

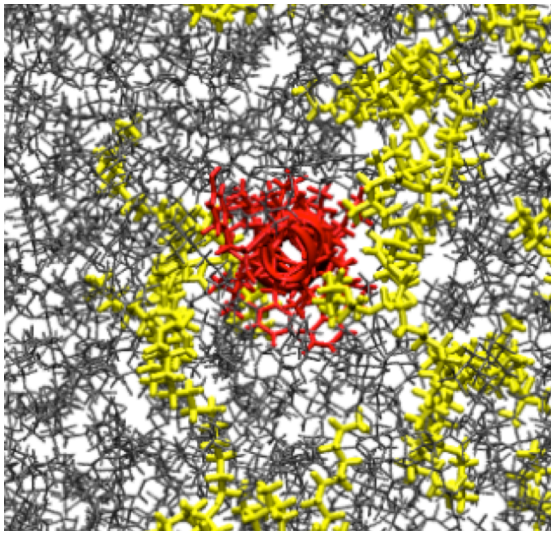

Figure 1. Interactions between ether lipids (yellow) and p24 transmembrane domain (red) in a POPC (gray) bilayer.

Ether lipids are important components of lipid membranes, constituting the 20% of the total phospholipid pool in mammals. While their structure is very similar to classical phospholipids, the presence of an ether link confers different structural and functional properties to this class of lipids1. Our metabolic studies coupled with targeted lipidomics show a crosstalk between phosphatidylcholine (PC) ether lipids and the sphingolipid synthesis pathways. Using in silico and in vitro techniques, we measured biophysical properties of ether lipids in POPC bilayers and their interactions with sphingolipids, in particular ceramide. Our results show that sphingolipids and ether lipids regulate the same membrane properties but do not interact with each other. Further in vivo studies show for the first time the involvement of ether lipids in the COPI vesicular transport via p24, a protein that has been shown to interact specifically with sphingomyelin 18:0 (SM 18)2. Our molecular dynamics simulations show a synergic interaction of ether lipids and SM 18 in binding to the transmembrane domain of p24. Overall, these results unveil a new role of ether lipids in cellular homeostasis.

Email: valeria.zoni@unifr.ch

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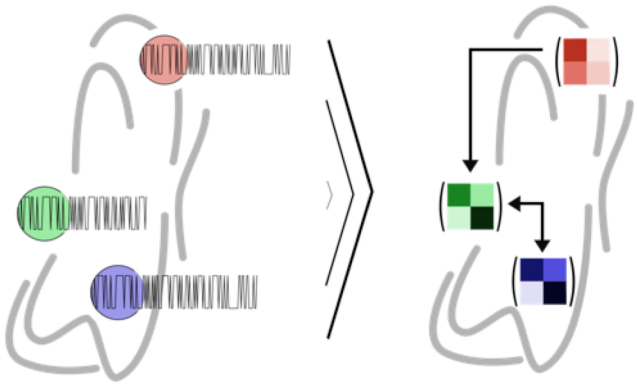
Information transfer between local Markov models evaluated for signaling protein

Tim Hempel[1], Nuria Plattner[1], Frank Noé[1]

1. Freie Universität Berlin, Institute of Mathematics and Computer Science, Arnimallee 6, 14195 Berlin, Germany

Markov state models (MSMs) are the state-of-the-art approach to combine vast numbers of short off-equilibrium molecular dynamics (MD) trajectories [1]. In recent years, MSM methodology has contributed significantly to pushing the timescales of MD simulations into the biologically relevant magnitude [2, 3]. However, modeling larger proteins with MSMs is often hampered by the difficulty to connect diverse scales of molecular activity. For large systems that incorporate almost independent processes, MSMs are often difficult to estimate and to interpret. Both problems can be mitigated by Markov state modeling of local protein features and estimating directional networks between them. In our work, we borrow tools from information theory where data-based inference of networks of spatially separated dynamic entities is a well-studied problem. We evaluate non-linear methods such as transfer entropy and mutual information and study their behavior and fitness for modeling MD simulation data by augmenting them with Markov state modeling. We apply our approach to the C2A domain of Synaptotagmin-1, a Calcium sensor in the neural exocytosis machinery. Our analyses include the conformational dynamics of active protein sites and information transfer between them. Besides developing a mechanistic model for the C2A domain, our goal is to describe molecular cooperativity beyond linear measures (such as correlation analyses) and to find the timely order of events to better understand allosteric mechanisms. We thereby aim at mitigating scaling problems in Markov modeling while improving biological interpretability.



Email: tim.hempel@fu-berlin.de

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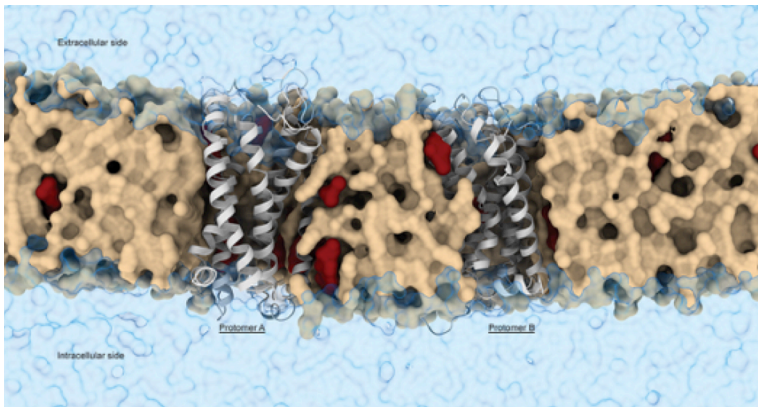
A Comprehensive Description of the Homo and Heterodimerization Mechanism of the Chemokine Receptors CCR5 and CXCR4

Di Marino Daniele[1], Motta Stefano[2], Limongelli Vittorio[1]

1. Faculty of Biomedical Sciences, Institute of Computational Science, Università della Svizzera Italiana (USI), via G. Buffi 13, 6900 Lugano, Switzerland.
2. Department of Earth and Environmental Sciences, University of Milano Bicocca (DISAT), p.za della Scienza 4, 20126 Milan, Italy.



The chemokine receptors belong to the G Protein Coupled Receptors (GPCRs) protein family and they are mostly involved in the functioning and maintenance of the immune system. This class of GPCRs represents a crucial target for a therapeutic approach in a wide range of inflammatory and autoimmune diseases. Furthermore, in several cardiac disorders and in the HIV infection a key function of these receptors was also demonstrated. Very recently high expression levels of these receptors were experimentally correlated with the metastatization process in different types of cancers. The human genome encodes for nineteen chemokine receptors. Among them, CXCR4 and CCR5 are two of the mainly studied since they play crucial roles in different severe pathologies. For instance, the inhibition of the CCR5-CXCR4 heterodimer formation reduces atherosclerosis in a hyperlipidemic mouse model, whereas type 1 HIV requires CXCR4 and CCR5 as co-receptors to enter the host cells. In this scenario, the use of computational techniques able to describe complex biological processes, such as protein dimerization, acquires a great importance.
Here we have used a new enhanced sampling method called CG-MetaD where the coarse-grained (CG) description of the systems is combined with well-tempered metadynamics (MetaD). This methodology is particularly suitable to describe complex biological processes that happen in a time scale beyond the seconds. We report for the first time a total of ~5.5 milliseconds of CG-MetaD simulations describing the homo and heterodimerization mechanism of CCR5 and CXCR4. In our extensive CG-MetaD simulations we have captured multiple association and dissociation events of the two receptors in membrane, thus computing a detailed free energy landscape of the entire dimerization process.
Our theoretical study reveals critical motions and important structural-dynamical features that are at the basis of the homo- and heterodimer formation allowing to link the dimerization process with the GPCRs activation mechanism. Our results pave the road to understand a possible general mechanism of GPCRs dimerization in membrane with particular attention for future drug development and applications.

Email: daniele.di.marino@usi.ch

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A Coarse-Grained Molecular Dynamics approach to aqueous polypeptide coacervates

Maria Tsanai, S.J Marrink.[1]

1. Groningwn Biomolecular Sciences and Biotechnology Insitute, University of Groningen, Nijenborgh 7, 9747 AG Groningen, The Netherlands

Coacervation is a unique type of electrostatically-driven liquid-liquid phase separation, resulting from association of oppositely charged macro-ions typically in aqueous solution with a high concentration of salt (0.1–4 M) [1] In this project, we use coarse-grained molecular dynamics (CGMD) simulations to establish coacervate phase diagrams in order to understand the fundamental driving forces of coacervate formation. We focus on canonical systems composed of oppositely charged peptides (e.g., polylysine, polyglutamate) for which experimental phase diagrams are available. [2] To this end, we will make use of the forthcoming Martini 3.0 model [3] which is an example of a CG force field that has been widely applied to study a large variety of biomolecular processes.

Keywords: Coacervates, polylysine, polyglutamate, coarse-grained molecular dynamics, MARTINI model.

Email: m.tsanai@rug.nl

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Stability of LD contact site

Laura Endter[1] and Herre Jelger Risselada[1]

1. Institute nstitute of Theoretical Physics, Georg-August-Universit¨at Göttingen, Friedrich-Hund-Platz 1, 37077 Göttingen

Lipid Droplets (LDs), although long time unterated in its role in eukaryotic cells, have now emerged to be extensiveley studied and still pose intriguing questions to the researchers engaged in unraveling their secrets. Being closely linked to regulatory processes regarding the lipid metabolism and homeostasis they are not only fascinating objects in a biophysical point of view but are also a possible target for medical apllications for pathological conditions such as obesity and diabetes [1, 2]. Once formed, the LD phospholipid monolayer appears to stay in close contact with the lipid bilayer of the endoplasmic reticulum. Aiming to determine the stability of the LD connection to the endoplasmic reticulum (ER) and the influ- ence of seipin on that contact side we deploy coarse grained simulations using the Martini model. With calculations of free energy differences [3, 4] and barriers we may be able to shed some light on the question of the nature of the structure and the mechanistic pathway of formation and maintainace of the LD-ER contact site.

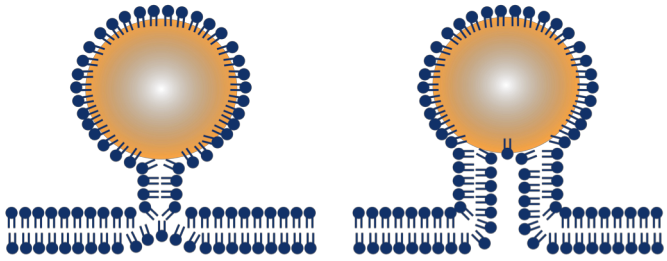

Figure 1. Sugesstion for possible structures of the lipid droplet-endoplasmic reticulum contact site.

Email: laura.endter@theorie.physik.uni-goettingen.de

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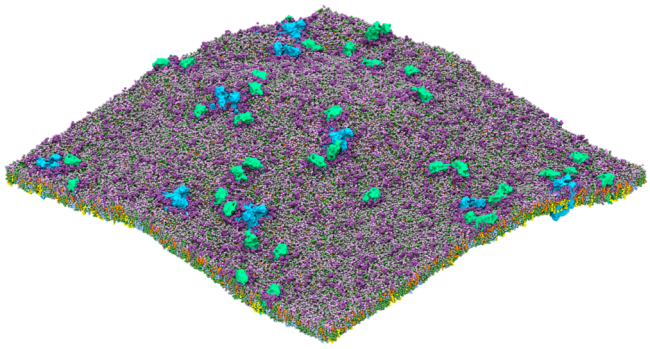
Multiscale molecular dynamics to explore voltage-gated sodium channel oligomerisation

William Glass[1] and Philip C. Biggin[1]

1. Department of Biochemistry, University of Oxford, Oxford, UK



Electrical signalling is key to a vast number of biological processes within the nervous system and for this to occur, specific types of transmembrane proteins, named voltage-gated ion channels, are utilised[1]. Voltage-gated Sodium ion (Nav) channels are vital to the correct function of nerve cells for the effective transmission of an action potential. Typically, Nav channels are not present in isolation and are known to be associated with one or more β-subunits[2]. These transmembrane proteins are multifunctional and interact with the main α-subunit of the Nav channel in addition to having a cell adhesion function through their extracellular immunoglobulin domain. In Nav1.5 the β3-subunit is known to non-covalently interact with the central α-subunit[3], however the exact mode of interaction is unclear. Additionally, β3 has been found to form trimers within the membrane through interactions between the extracellular Ig domains as well as cross-linking of α-subunits[4, 5]. To gain an insight into the α – β subunit relationship both atomistic and coarse grained molecular dynamics methodologies are adopted. Longer time scales granted through the latter technique allow the reported trimerisation and higher order oligomers to be studied and the likely interactions and dependence on domains reviewed. Increasingly large-scale simulations are beginning to elucidate the relationship between the β3-subunit and the central α-subunit and increase our understanding of ion channel function.

Email: william.glass@chem.ox.ac.uk

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The SAMPL6 SAMPLing challenge: Assessing reliability and efficiency of binding free energy calculations

Andrea Rizzi,[a,b] Travis Jensen,[c] David R. Slochower,[d] Stefano Bosisio,[e] Matteo Aldeghi,[f] Alex Dickson,[g,h] Bert L. de Groot,[f] Julien Michel,[e] Michael K. Gilson,[d] Michael R. Shirts,[c] David L. Mobley,[i] John D. Chodera[a*]

[a] *Computational and Systems Biology Program, Sloan Kettering Institute, New York, NY 10065;* [b] *Tri-Institutional Training Program in Computational Biology and Medicine, New York, NY 10065;* [c] *Department of Chemical and Biological Engineering, University of Colorado Boulder, Boulder, CO 80309;* [d] *Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego, USA;* [e] *EaStCHEM School of Chemistry, University of Edinburgh, David Brewster Road, Edinburgh EH9 3FJ, UK;* [f] *Max Planck Institute for Biophysical Chemistry, Computational Biomolecular Dynamics Group, Göttingen, Germany;* [g] *Department of Biochemistry and Molecular Biology, Michigan State University, East Lansing, MI, USA;* [h] *Department of Computational Mathematics, Science and Engineering, Michigan State University, East Lansing, MI, USA;* [i] *Department of Pharmaceutical Sciences and Department of Chemistry, University of California, Irvine, California 92697, USA.*

We present the conceptualization and results for the first SAMPLing challenge from the SAMPL series focusing on the assessment of convergence properties and reproducibility of binding free energy methodologies. We provided parameter files and multiple initial geometries for two octa-acid (OA) and one cucurbit[8]uril (CB8) host-guest systems, for which it is computationally feasible to obtain converged binding affinity estimates in a matter of hours or a few days. Participants submitted binding free energy predictions as a function of the computational effort for six different alchemical- and physical-pathway (e.g. molecular dynamics and potential of mean force) methodologies based on GROMACS, AMBER, and OpenMM implementations. For the two small OA binders, the free energy estimates computed with alchemical and potential of mean force approaches show relatively similar variance and bias as a function of the number of energy/force evaluations, with the attach-pull-release (APR) and GROMACS expanded ensemble methodologies performing particularly well. The differences between the methods widen when analyzing the CB8-quinine system, where both the guest size and correlation times are greater. For this system, coupled topologies non-equilibrium switching (CP-NS) obtained the overall highest efficiency followed by Hamiltonian replica exchange (HREX). Among the conclusions emerging from the data, we found that CP-NS convergence can be enhanced by increasing the length of the non-equilibrium protocol, that HREX, while displaying very small variance, can incur into substantial bias that depends on the initial population of the replicas, and that the Berendsen barostat introduces non-negligible artifacts in expanded ensemble simulations. Surprisingly, the results suggest that specifying the force field parameters and charges is insufficient to ensure reproducibility to better than ~0.5 kcal/mol. Further work will be required to identify the exact source of these discrepancies.

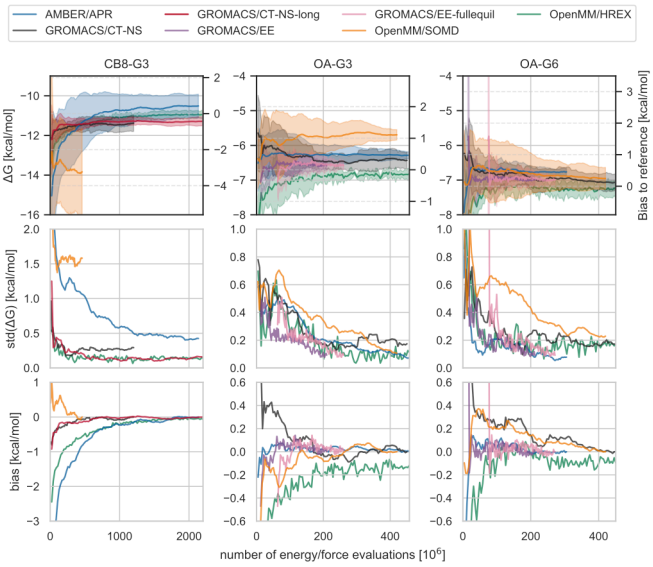


Fig. 1. ***Free energy, standard deviation, and bias as a function of computational cost.***

Email: andrea.rizzi@choderalab.org

Attraction between like-charged proteins: A theoretical study of β-lactoglobulin dimer

Rakesh Srivastava,[1] Pradipta Bandyopadhyay[1]

1. School of Computational and Integrative Sciences, Jawaharlal Nehru University, New Delhi, India

Like charge attraction in an aqueous medium containing salt is known to be important in various molecular interactions in biological systems e.g. DNA condensation, liposomal aggregation, like charged protein subunits binding etc. In the absence of any salt at pH 3.0, β-lactoglobulin exists predominantly in monomeric form carrying +13e charge but dimerization gets favored as a salt is added to the system. In this work, binding free energy variation of β-lactoglobulin dimerization as a function of NaCl concentration at pH 3.0 has been studied using molecular mechanics-three dimensional reference interaction site model (MM-3DRISM) theory. RISM is an Ornstein-Zernike equation based integral equation theory, developed by Chandler et al (1972) for molecular liquids firmly based on statistical mechanics. The 3D-RISM theory is an extension of RISM proposed by Beglov et al (1997), in which pair correlation function of solvent-solute sites are determined for fixed solute geometry and from the pair correlation function, thermodynamic quantities can be calculated. We have combined 3D-RISM and Molecular dynamics (MD) simulation to get the solute fluctuation. Free energy of binding between two monomers was calculated using the 3D- RISM method on selected snapshots from our MD trajectory. Our results show that the binding free energy of β-lactoglobulin dimerization initially decreases with increasing salt concentration and then gets saturated. This qualitative finding is in agreement with the earlier experimental work of Sakurai et al(2001). It has also been found that the Cl- ions are responsible for supporting the dimer formation and Cl- ion density around monomers increases in the dimer as compared to around monomeric forms before dimerization which suggests that the Cl- ions screen the electrostatic repulsion between monomers in the dimer (Fig.1). Further, the Na+ and Cl- ion density near the binding interface remain almost similar before and after binding. Moreover, this study also reveals that the hydrogen bonds between the β-strands of two monomers at the binding interface, water- mediated hydrogen bonds near the binding interface and hydrogen bonds between the two loops containing Asp33 of monomers play important role in dimer stabilization.

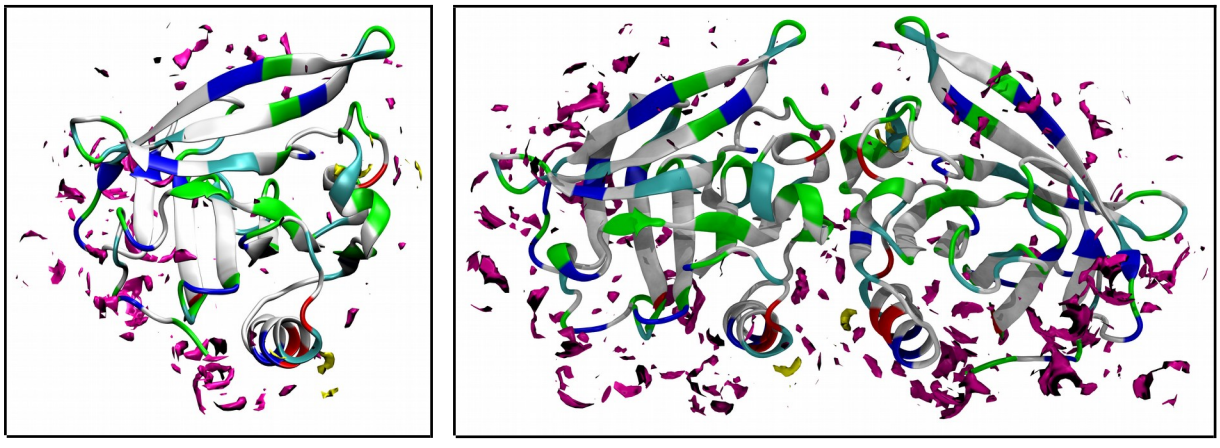


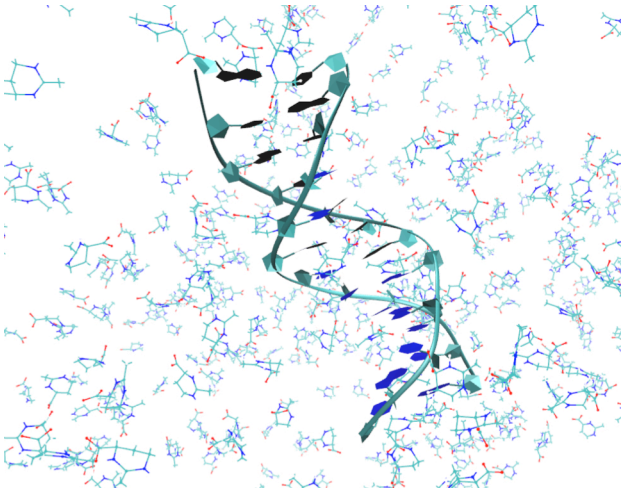
Figure 1. Cl- and Na+ ion pair correlation function (g(r)) obtained from MM-3DRISM calculation around monomer before dimerization and around dimer. The densities shown represent g(r) values 10.0 and more. Cl- ion density has been shown with magenta color and Na+ ion density with yellow color. In the protein cartoon, blue, red, green, cyan and white colors represent basic, acidic, polar, protonated Asp and non-polar residues respectively.

Email: rakesh26_sit@jnu.ac.in

Interaction of single- and double-stranded DNA with ectoine in the light of Kirkwood-Buff theory and local/bulk partitioning model: a Molecular Dynamics study

Ewa Anna Oprzeska-Zin,[1] Jens Smiatek[2]

1. Institute for Computational Physics University of Stuttgart (DE)
2. Forschungszentrum Jülich, Helmholtz Institute Münster: Ionics in Energy Storage Corrensstrasse 46 48149 Münster (DE)



In nature, the cellular environment of DNA composes not only of water and ions, but also of salts, lipids and other co-solutes, which can exert both stabilizing and destabilizing influence on the formation and existence of particular DNA higher-order forms [1]. Among them, ectoine, known as osmoprotectant occurring naturally in halophilic bacteria and other microorganisms exposed on severe osmotic stress [2, 3], turns out to be of particular importance. Ectoine has been shown to act as a stabilizer for proteins [4, 5], which are typically uncharged. However, the evidence on ectoine interaction with DNA, bearing a pronounced negative charge, is very limited.

In our research we investigate the behavior of a short single-stranded 7-bp DNA oligonucleotide with the sequence d(GCGAAGC) in both linear and folded form [6], as well as 24-bp B-DNA duplex [7] in aqueous solution with various concentrations of ectoine. With the application of Kirkwood-Buff theory [8, 9] and Local/Bulk Partitioning Model [10] we elucidate the thermodynamic details of DNA-ectoine interactions. Although ectoine has been commonly considered as a stabilizing agent for biomolecular structures, our results demonstrate the ectoine-DNA conformation-dependent binding behavior, driven by enthalpic interaction forces. This allows us to rationalize the DNA structure destabilizing influence of ectoine.

Email: ewa.zingrebe@icp.uni-stuttgart.de

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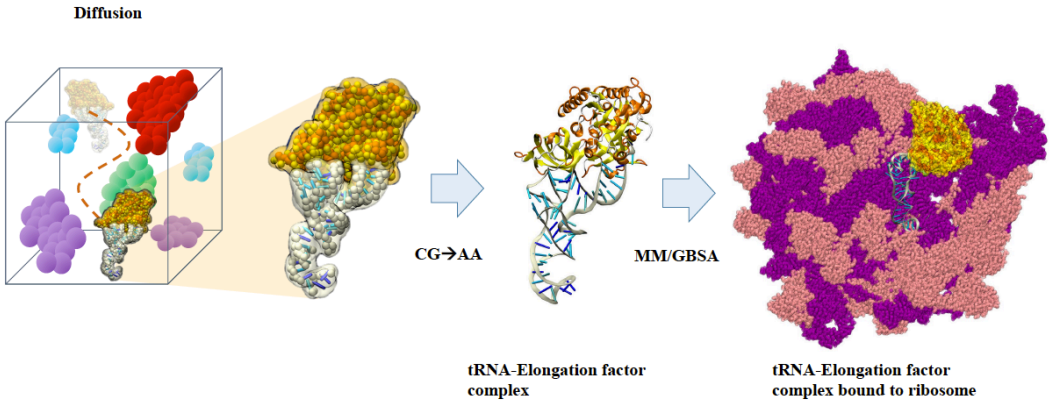
A Multiscale Modeling Approach To Understanding The Effect Of Macromolecular Crowding On Protein Translation

V. P. Srikanth Kompella[1,2], Ian Stansfield[3], M. Carmen Romano[2,3] and Ricardo L. Mancera[1]

1. School of Pharmacy and Biomedical Sciences, Curtin Health Innovation Research Institute and Curtin Institute for Computation, Curtin University, GPO Box U1987, Perth WA 6845, Australia
2. Institute for Complex Systems and Mathematical Biology, Physics Department, University of Aberdeen, Aberdeen, UK.
3. Institute of Medical Sciences, University of Aberdeen, Aberdeen, UK

The environment inside cells is different from that of dilute conditions, under which the majority of in vitro experiments are performed. A typical cell has a macromolecular concentration of 100-450 g/L with 5-40% of its volume occupied by macromolecules. This large concentration of macromolecules affects their diffusion and that of metabolites and other biomolecules. During protein synthesis a tRNA molecule with an attached amino acid reaches the acceptor site (A-site) of the ribosome and delivers its amino acid, after which the ribosome hops to the next codon. The tRNAs that bind to the ribosome are in ternary complexes with other proteins, and the diffusion of these protein complexes is much slower in the crowded environment of the cytoplasm, in turn affecting the translation process. The magnitude of the effect of the slow diffusion of tRNAs on the hopping rates of the ribosome depends on the competition between cognate, non-cognate and near-cognate tRNAs at the A- site. In order to study quantitatively the role of macromolecular crowding on the diffusion of tRNAs, a coarse-grained molecular dynamics simulation approach is being undertaken employing the MARTINI forcefield. Predictions of binding affinity of cognate, non-cognate and near-cognate tRNAs to the ribosome, using the MM/GBSA approach, will also be undertaken to characterise the competition between them. The predictions of these calculations will then be used to perform a cell system-level stochastic dynamics simulation to understand the dynamics and organization of protein translation.



Email: v.kompella@postgrad.curtin.edu.au

Local Structure of Methylated Region in DNA

Gyehyun Park, YounJoon Jung

1. Department of Chemistry, Seoul National University, Seoul 08826, Korea

DNA methylation is a key process in the gene expression controlling the activity of chromatin and regulating the transcription. Interestingly, DNA methylation has been reported to alter the interaction between a nucleosome and a DNA strand. In particular, the affinity between them is significantly reduced near methylated (CpG)3 by the point mutation process. [1,2,3] To explain the relation between DNA methylation and nucleosome positioning, we investigated the structural anisotropy of a highly curved DNA molecule by cytosine methylation via molecular dynamics simulation using an all-atom model. The cytosine methylated region shows an energetically stable structure compared to non-methylated counterpart in the same DNA strand. The breakdown of hydrogen bonds, reduction of helix rotation angle, and mismatched π-π stacking are observed in the non-methylated region. As the number of methylation nucleobases increases in the strand, the denaturation of localized domain within the DNA is amplified. Our study shows a clear evidence that methylation changes the local structure of DNA, which can be the factor of controlling nucleosome positioning.

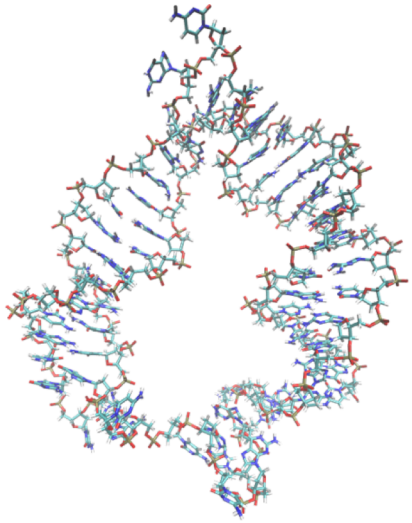


Figure 1. Simulation snapshot of cyclic DNA to model bent DNA

Email: kyehyun3950@snu.ac.kr

References

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Enhancing industrial bioprocesses in yeast via membrane optimization

Josef Melcr, Siewert-Jan Marrink

1. University of Groningen, The Netherlands

With ever-growing concerns about environmental sustainability we need alternatives to traditional, fossil-fuel based chemical production. Cell factories, which use microorganisms to produce materials from renewable biomass, are an attractive alternative. Such “green factories” are expected to have a transformative impact in industrial biotechnology, however, high-yield cell factory strains that can produce commercially viable amounts of product are yet to be developed and optimized. The currently sub-optimal product output is due to the inherently toxic conditions arising from the chemical production itself. [1,2] The plasma membrane is the first shield guarding the cells from the growing toxic environment. Hence, the plasma membrane is our target for a rational optimization in terms of their lipid and protein content. [3-6] In this contribution, I will present the ongoing development in the building of a realistic yeast plasma membrane with an asymmetric distribution of lipids in its inner/outer leaflets. I will compare our preliminary results on optimizing simple symmetric membranes for their resistance against chemical agents from molecular simulations with experimental trends from liposomes.

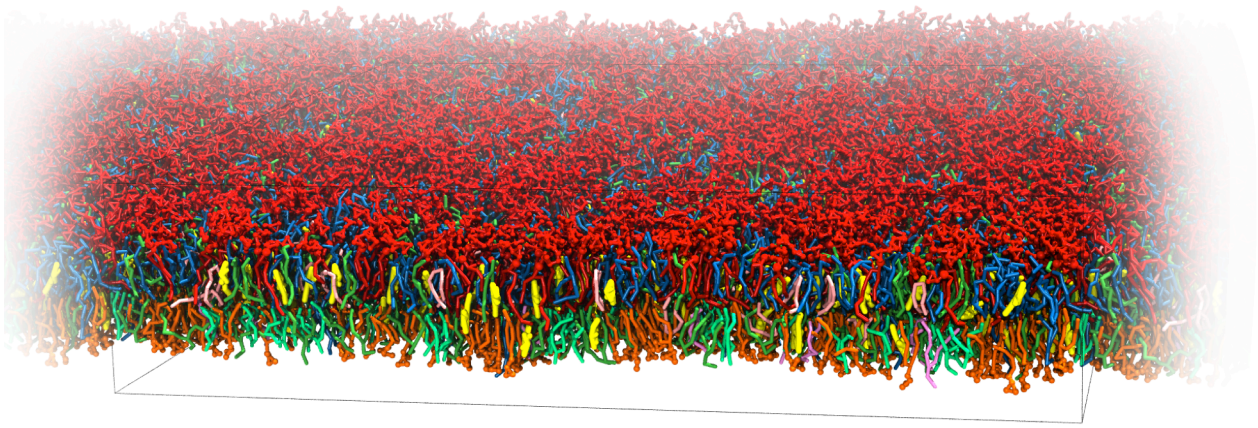

Figure 2. Simulation model of a yeast lipid plasma membrane. Composition based on [7,8].

Email: jmelcr@gmail.com

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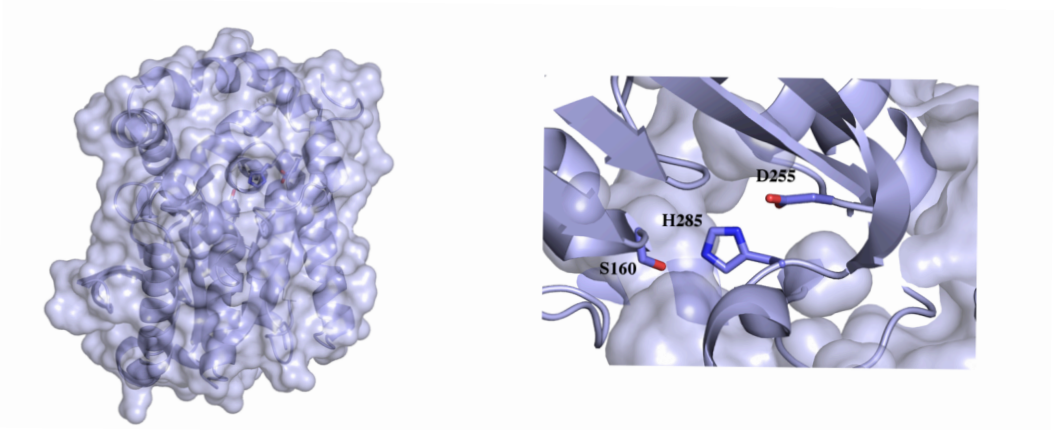
QM/MM studies on a thermophilic esterase

Beatriz Almeida[1], Alexandra Teresa Pires Carvalho[1]

1. Center for Neuroscience and Cell Biology, Institute for Interdisciplinary Research (IIIUC), University of Coimbra



Over the years, some biodegradable polymers (e.g. aliphatic polyesters) have been popularized and continuously studied due to their good mechanical properties and compatibility for biomedical applications 1,2. Various lipases can be employed in ring-opening polymerization (ROP) of biodegradable polymers. However, these enzymes are not well suited for the reaction conditions required in industrial preparations, such as high temperatures and exposure to organic solvents and do not produce materials with the desired properties. With this in mind, customized serine hydrolases can provide the right green alternative for the biosynthesis of higher value polymers 2. These enzymes are characterized by a α/β hydrolase fold and a catalytic triad consisting of an aspartate (Asp) or glutamate (Glu) residue, a histidine (His) and a nucleophilic serine (Ser) residue 3. In this work we studied the catalytic mechanism of the hyperthermophilic archaeon Archaeoglobus fulgidus (AFEST) esterase using Quantum Mechanics/Molecular Mechanics (QM/MM) methods 4. AFEST is a promising candidate for potential industrial applications, because of its broad substrate specificity and high stability 5.

Email: beatrizcolumbanoalmeida@gmail.com

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1. Shiro Kobayashi and Akira Makibo, Enzymatic Polymer Synthesis: An Opportunity for Green Polymer Chemistry. Chemical Reviews, Volume 109, 2009, Pages 5288-5353.
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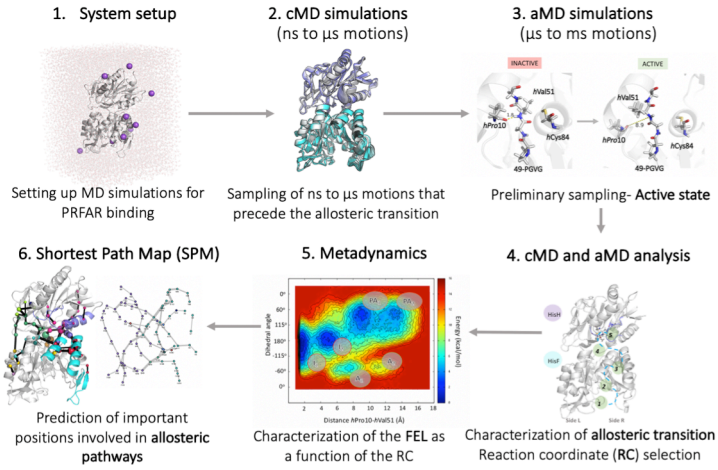
Unraveling the millisecond allosteric activation of imidazole glycerol phosphate synthase (igps)

Carla Calvó-Tusell,[1] Miguel A. Maria-Solano,[1] Ferran Feixas,[1] Javier Iglesias-Fernández,a Sílvia OsunA[1,2]

1. Institute of Computational Chemistry and Catalysis and Department of Chemistry, University of Girona, E-17003 Girona, Catalonia, Spain.
2. ICREA, Pg. Lluís Companys 23, 08010 Barcelona, Spain



Allostery is an intrinsic property of proteins generally described as the process by which the effect of binding at one site is transmitted to another, often distal, functional site, allowing for activity or function regulation.[1] Exploring the mechanisms of allosteric regulation is important to understand biological processes such as enzyme catalysis, cell signaling or the molecular basis of disease. Allosteric transitions require the order of microsecond to second timescales. Imidazole Glycerol Phosphate Synthase (IGPS) is an heterodimeric enzyme complex widely used as a model to study allosteric regulation between subunits. Previous studies based on NMR experiments reported that the allosteric activation of IGPS, promoted by the binding of an effector, takes place in the millisecond timescale.[2] However, the active structure of IGPS has not been yet characterized.[2,3] Computational methods are used to study allostery, but obtaining enough conformational sampling to completely characterize allosteric events represents a challenge for current simulation techniques.[4]

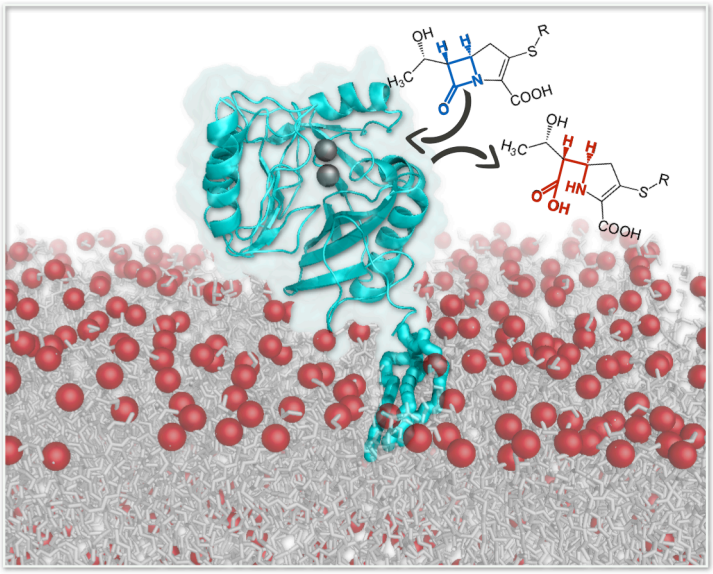
In this work, the millisecond allosteric activation mechanism of IGPS is unraveled step by step by means of a combination of simulation techniques. First, nanosecond to microsecond motions that initiate the allosteric signal transmission are deciphered by means of conventional Molecular Dynamics (cMD). Second, accelerated Molecular Dynamics (aMD) is used to sample events that occur in the microsecond to millisecond timescale, including the complete characterization of IGPS allosteric activation and the active structure (characterized by the formation of an oxyanion hole). Third, the active state obtained with aMD is used to select the proper reaction coordinate to reconstruct the free energy landscape of the activation process by metadynamics. Finally, the allosteric communication pathway is traced through key residues for IGPS function and allostery using our Shortest Path Map tool.[5] In summary, we have been able to computationally characterize the activation mechanism of IGPS by applying a computational protocol designed to describe and characterize complex long timescale motions. This protocol can be generalized to study the activation mechanism of other allosterically regulated enzymes.

Email: carla.calvo.tusell@gmail.com

Molecular Dynamics Simulations Shed a Light on the Relationship between Membrane Anchoring and the Antibiotic Resistance Mechanism of New Delhi Metallo-β-Lactamase 1.

Alessio Prunotto[1], Guillermo Bahr[2], Lisandro Gonzàlez[2], Alejandro J. Vila[2], Matteo Dal Peraro[1]

1. Laboratory for Biomolecular Modeling, École Polytechnique Fédérale de Lausanne, Switzerland
2. Instituto de Biologia Molecular y Celular de Rosario, Argentina



Metallo-β-Lactamase 1 (NDM-1) is a bacterial enzyme that is able to provide drug resistance against a large range of last resort antibiotics.
Its catalytic action is mediated by two zinc ions present in the active site, which cause the hydrolysis of β-lactam antibiotics (such as penicillin derivatives, cephalosporins and carbapenems), hence causing their inactivation.
The presence of zinc ions is fundamental for the catalytic action of these enzymes: the common reaction of the immune system consists in using calprotectins to induce zinc starvation, hence retrieving zinc ions and limiting the enzymatic activity.
However, in the last years, NDM1 was reportedly associated to several outbreaks of bacterial infections resistant to antibiotic treatment: specifically, studies showed that drug resistance is due to the presence of a post-translationally modified version of NDM-1. In particular, the lipidation of a cysteine in the N-terminal region is able to drive the anchoring of NDM-1 to the bacterial membrane. Membrane anchoring can in turn prevent the inactivation of NDM-1 with a mechanism that is still object of debate.
Molecular dynamics simulations, conducted both at a coarse-grain and at an atomistic level, shed a light on the properties of NDM-1 that allowed to develop this unique mechanism.
In particular we highlight that the natural affinity of non-lipidated NDM-1 for the membrane, if compared to other enzymes of the same class, such as VIM-2, is the driving force which allowed the appearance of this peculiar mechanism.
Moreover, we identified the lipid composition of the bacterial membrane as one of the elements that guarantees the correct action of membrane binding: in particular, the presence of charged lipids, especially cardiolipins, is fundamental to drive the membrane recognition and successive anchoring.

Email: alessio.prunotto@epfl.ch

6 Participant list

Organizers

Giulia Palermo
University of California Riverside, United States
giulia.palermo@ucr.edu

Valentina Tozzini
Istituto Nanoscienze CNR, Italy
valentina.tozzini@nano.cnr.it

Matteo Dal Peraro
Swiss Federal Institute of Technology Lausanne, Switzerland
matteo.dalperaro@epfl.ch

Rommie E. Amaro
University of California San Diego, United States
ramaro@ucsd.edu

Alexandre Bonvin
Utrecht University, The Netherlands
a.m.j.j.bonvin@uu.nl

Participants

Siewert J. Marrink, s.j.marrink@rug.nl
Vittorio Limongelli, vittoriolimongelli@gmail.com
Ivaylo N. Ivanov, iivanov@gsu.edu
Rebecca Wade, rebecca.wade@h-its.org
Gary Huber, gahuber95@gmail.com
Gregory Voth, gavoth@uchicago.edu
Martin Zacharias, martin.zacharias@mytum.de
Alessandra Magistrato, alema@sissa.it
Cristian Micheletti, michelet@sissa.it
Giorgia Brancolini, giorgia.brancolini@nano.cnr.it
Steffen Lindert, lindert.1@osu.edu
Michele Cascella, michele.cascella@kjemi.uio.no
Helmut Grubmüller, hgrubmu@gwdg.de
Zaida (Zan) Luthey-Schulten, zan@illinois.edu
Giovanni Pinamonti, giopina88@gmail.com
Adrian Mulholland, adrian.mulholland@bristol.ac.uk
Joanna Trylska, jtrylska@ucsd.edu
Thomas Steinbrecher, thomas.steinbrecher@schrodinger.com
Stefano Vanni, stefano.vanni@unifr.ch

Angelo Rosa, anrosa76@gmail.com
Yinglong Miao, yinglong.miao@gmail.com
Walter Rocchia, walter.rocchia@iit.it
Simon Olsson, solsson@zedat.fu-berlin.de
Clarisse G. Ricci, cla.g.ricci@gmail.com
Paolo Carloni, p.carloni@fz-juelich.de
Ursula Rothlisberger, ursula.roethlisberger@epfl.ch
Holger Gohlke, gohlke@uni-duesseldorf.de
Marco De Vivo, marco.devivo@iit.it
Benjamin Jagger, bjagger@ucsd.edu
Deniz Aydin, d.aydin@epfl.ch
Luca Monticelli, luca.monticelli@inserm.fr
Natalia Ostrowska, n.ostrowska@cent.uw.edu.pl
Jean-Philip Piquemal, jpp@lct.jussieu.fr
Hender Lopez, hender.lopezsilva@ucd.ie
Soundhararajan Gopi, soundharar@gmail.com
Simon L. Dürr, simon.durr@epfl.ch
Weria Pezeshkian, weria.pezeshkian@gmail.com
Mahdi Bagherpoor Helabad, mbagerpoor@zedat.fu-berlin.de
Pedro Figueiredo, pmrfigueiredo@cnc.uc.pt
Riccardo Capelli, riccardo.capelli@icrm.cnr.it
Francesco Delfino, delfinofrancesco90@gmail.com
Fabian Grunewald, f.grunewald@rug.nl
Kai Steffen Stroh, kai.stroh@theorie.physik.uni-goettingen.de
Haleh Abdizadeh, h.abdizadeh@rug.nl
Cristina Paissoni, cristina.paissoni@gmail.com
Mathieu Fossépré, mathieu.fossepre@umons.ac.be
Valeria Zoni, valeria.zoni@unifr.ch
Tim Hempel, tim.hempel@fu-berlin.de
Daniele Di Marino, daniele.di.marino@usi.ch
Maria Tsanai, m.tsanai@rug.nl
Laura Endter, laura.endter@theorie.physik.uni-goettingen.de
William Glass, william.glass@chem.ox.ac.uk
Andrea Rizzi, andrea.rizzi@choderalab.org
Rakesh Srivastava, rakesh26_sit@jnu.ac.in
Ewa Anna Oprzeska-Zin, ewa.zingrebe@icp.uni-stuttgart.de
V. P. Srikanth Kompella, v.kompella@postgrad.curtin.edu.au
Gyehyun Park, kyehyun3950@snu.ac.kr
Josef Melcr, jmelcr@gmail.com
Beatriz Almeida, beatrizcolumbanoalmeida@gmail.com
Carla Calvó-Tusell, carla.calvo.tusell@gmail.com
Alessio Prunotto, alessio.prunotto@epfl.ch

7 Location

The CECAM Headquarters is located at the École polytechnique fédérale de Lausanne (EPFL)

How to get to EPFL from Lausanne CFF railway station

There is a metro link very close to the Lausanne train station, across the main exit:

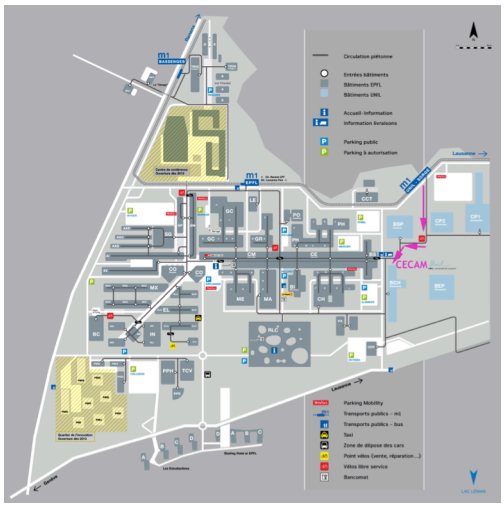
1. Take the **metro M2** towards “Croisettes” and then exit at “Lausanne Flon” (the first stop after the train station stop “Lausanne Gare”).
2. From “Lausanne Flon”, take the **metro M1** towards “Renens Gare” and exit at stop “UNIL-Sorge”.

How to get to EPFL from Renens CFF railway station

You may choose to stop at Renens Gare (also called Renens CFF) station. Form there, take the metro towards “Lausanne Flon” and exit at stop “UNIL-Sorge”.

How to get to CECAM from UNIL-Sorge metro station

Once you arrive at UNIL-Sorge, cross the street and follow the path indicated on the map: you will arrive straight at the entrance of the CECAM Seminar Zone (2nd floor of the Batochime), where the Workshop will be held.



8 Lunch on campus

There are many cafeterias on EPFL campus walking distance from CECAM.

See map below:

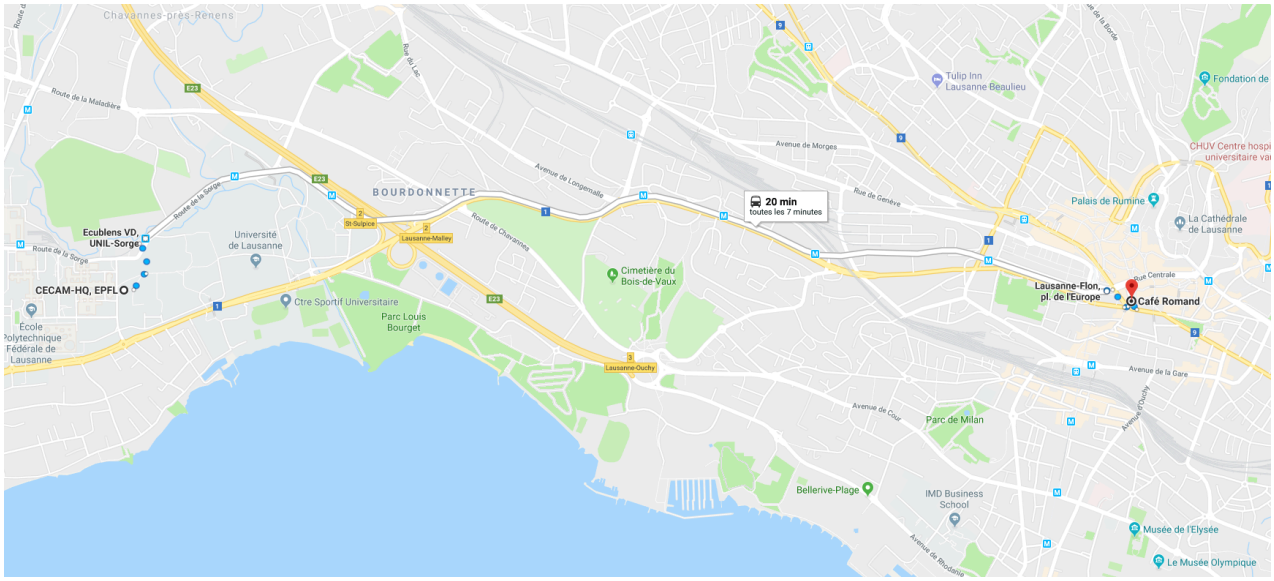
9 Social Dinner

Dinner will take place at Le Café Romand on 5 February 2019 at 20.00

Le Café Romand
Place Saint-François 2
1003 Lausanne
http://www.cafe-romand.ch/

How to get to Le Café Romand:

From CECAM take the Metro M1 direction Lausanne Flon from stop "UNIL-Sorge" and get off at "Lausanne Flon" stop. Then you have a 5 minute walk until you reach Le Café Romand on Place Saint-François.



Please confirm your attendance to the social dinner by completing the registration form in the coffee break room when you arrive at the workshop for registration.

Let us know of any intolerances or allergies you may have.

10 Additional information

WIFI code during your event:

SSID: PUBLIC-EPFL

Website: Enclair.epfl.ch

Username: x-cecamguest

Password: *fonpan69*

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CECAM Website for this workshop:

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Your contact at CECAM:

Joanna Jermini-Howard: *EPFL, Lausanne, Switzerland, joanna.jermini@epfl.ch*