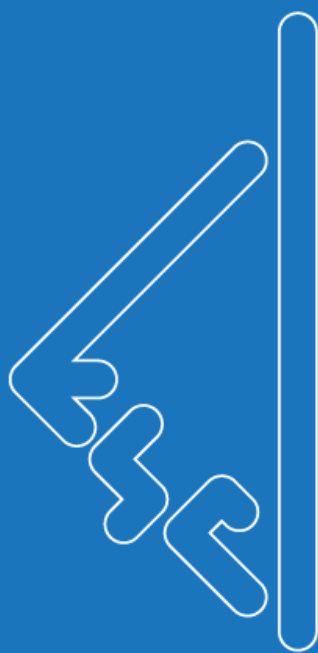# 2019

13 Mai
17 Mai

INSTITUT D'ÉTUDES SCIENTIFIQUES DE CARGÈSE

CHALLENGES IN LARGE SCALE BIOMOLECULAR SIMULATIONS 2019 BRIDGING THEORY AND EXPERIMENTS

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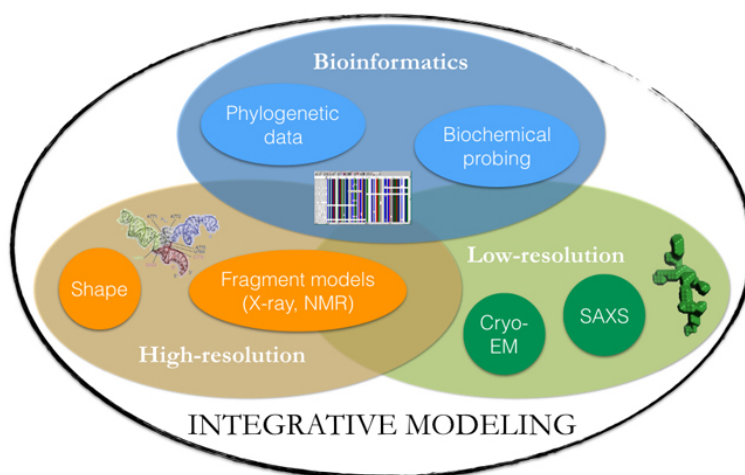Dominique Donzella
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INSTITUT D'ÉTUDES SCIENTIFIQUES DE CARGÈSE

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Challenges in Large Scale Biomolecular Simulations 2019 Bridging Theory and Experiments

Cargèse, France, 13-17 May 2019

Book of abstract

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Program

Monday, 13 May 2019

08:30 - 08:50	Registration
08:50 - 09:30	*Identification of protein functional regions* - Ivan Coluzza, CIC biomaGUNE, Spain
09:30 - 10:10	*Design of polymeric building blocks: Coarse graining, multiscale and theoretical predictions* - Barbara Capone, Roma Tre University, Italy
10:10 - 10:30	*Simulating T=1 and T=3 capsid self-assembly* - Dennis Rapaport, Department of Physics, Bar-Ilan University, Israel
10:30 - 10:50	**Coffee break**
10:50 - 11:30	*Membrane shredding, poration, and fusion studied with molecular simulations* - Ramachandra M Bhaskara, Max Planck Institute of Biophysics, Department of Theoretical Biophysics, Germany
11:30 - 12:10	*Atomistic Simulation of Biomolecular Function: Ribosomal Translation, Ligand Binding Heterogeneity, and a Dynasome Perspective* - Helmut Grubmüller, Max Planck Institute for Biophysical Chemistry, Theoretical and Computational Biophysics Department, Germany
12:10 - 14:00	**Lunch**
14:00 - 14:40	*Integrative, information-driven modelling of biomolecular complexes* - Alexandre Bonvin, Utrecht University, Faculty of Science (UU), Netherlands
14:40 - 15:20	*Theoretical Characterization of Protein Folding Dynamics: Connecting Atomist Model with Time-Resolved Spectroscopy Data* - Pietro Faccioli, University of Trento, Italy
15:20 - 15:40	*Accurate calculation of protein folding energetics by difference* - Javier Sancho, Institute for Biocomputation and Physics of Complex Systems (BIFI), Spain
15:40 - 16:10	**Coffee break**
18:30 - 19:30	**Cocktail**

Tuesday, 14 May 2019

08:50 - 09:30	*Leveraging structural data by decoupling structure thermodynamics and dynamics* - Frederic Cazals, ABS, France
09:30 - 10:10	*Multiscale Simulation of Protein Assemblies* - Gregory Voth, Department of Chemistry, James Franck Institute, and Institute for Biophysical Dynamics, The University of Chicago, Chicago, IL, USA
10:10 - 10:30	*Molecular Transport Through Nanopores: Bridging Simulations and Experiment* - Igor Bodrenko, Department of Physics, University of Cagliari, Italy
10:30 - 10:50	**Coffee break**
10:50 - 11:30	*Simulating nucleoprotein complexes: chromatin and ribosomes* - Karissa Sanbonmatsu, Los Alamos National Laboratory, USA
11:30 - 12:10	*Crowding in the cellular context: Tales of Clusters and Dynamics* - Michael Feig, Department of Biochemistry & Molecular Biology, Michigan State University, USA
12:10 - 14:00	**Lunch**
14:00 - 14:40	*Predicting the structure of RBP recognition elements* - Francois Major, Université de Montréal, Canada

14:40 - 15:00	*BZip transcription factors modulate DNA supercoiling transitions ? potential transcription regulatory mechanism: insights from molecular modelling* - Anna Reymer, Department of Chemistry and Molecular Biology, University of Gothenburg, Sweden
15:00 - 15:20	*MD simulation combined to fragment based approach for protein-peptide complex structure prediction* - Samuel Murail, CMPLI (Modélisation Computationnelle des Interactions Protéines-Ligand), France
15:20 - 15:40	Poster Flash Presentations
15:40 - 16:10	**Coffee break**

Wednesday, 15 May 2019

08:50 - 09:30	*Degeneracy in Molecular Scale Organization of Biological membranes* - Anand Srivastava, Molecular Biophysics Unit, Indian Institute of Science, Bangalore, India
09:30 - 10:10	*Focusing the Computational Microscope on Bacterial Cell Envelopes* - Syma Khalid, University of Southampton, United Kingdom
10:10 - 10:30	*Reweighted-Probability Enhanced Sampling: a reversed perspective on metadynamics* - Michele Invernizzi, ETH Zurich, Physics Department, Switzerland
10:30 - 10:50	**Coffee break**
10:50 - 11:30	*Combining computational and experimental approaches to comprehend the "how" and "why" of bacterial transcriptional regulation* - Peter Freddolino, University of Michigan, USA
11:30 - 12:10	*Understanding the interplay between RNA molecular flexibility, structure and chemical probing using all-atom molecular dynamics simulations* - Elisa Frezza, Cible Thérapeutique et Conception de Médicaments, Université de Paris
12:10 - 14:00	**Lunch**
14:00 - 14:40	*Multifunnel energy landscapes - how multiple functions are encoded in biomolecules* - Konstantin Roeder, University of Cambridge, UK
14:40 - 15:20	*Multiscale modelling of RNA and DNA structural motifs* - Filip Lankas, Department of Informatics and Chemistry, University of Chemistry and Technology Prague, Czech Republic
15:20 - 15:50	**Coffee break**
15:50 - 16:30	*Exploring RNA flexibility through a coarse-grained model and its coupling to experimental data* - Samuela Pasquali, Cible Thérapeutique et Conception de Médicaments, Université de Paris, France
16:30 - 16:50	*Exploring macromolecular machine mechanisms with numerical tools* - Chantal Prevost, Laboratoire de biochimie théorique, France

Thursday, 16 May 2019

| 08:50 - 09:30 | *Improving the performance of the RNA AMBER force field by tuning hydrogen bonding interactions* - Jiri Sponer, Institute of Biophysics of the Czech Academy of Sciences, Czech Republic |
| 09:30 - 10:10 | *Possibilities and current limitations of joining MD simulations and experiments: the cases of amyloid aggregation and membrane binding proteins* - Birgit Strodel, Jülich Research Centre, ICS-6: Structural Biochemistry, Heinrich Heine University Düsseldorf, Institute of Theoretical and Computational Chemistry, Germany |

10:10 - 10:30	*Getting divalent ion-biomolecule interactions right in Molecular Dynamics simulations* - Elise Duboué-Dijon, Laboratoire de biochimie théorique, France
10:30 - 10:50	**Coffee break**
10:50 - 11:30	*Combining diverse information and techniques to understand biological function* - Mara Prentiss, Harvard University, USA
11:30 - 12:10	*A Native Molecular View of Cells by Cryo-ET - Structural Biology Done In-Situ* - Philipp Erdmann, Max Planck Institute of Biochemistry, Germany
12:10 - 14:00	**Lunch**
14:00 - 18:00	**Excursion**
19:30 - 23:55	**Social Dinner**

Friday, 17 May 2019

08:50 - 09:30	*Towards a holistic view of DNA* - Modesto Orozco, IRB Barcelona, Spain
09:30 - 10:10	*Multi-Scale Simulations Yield Insight into Protein Diffusion and Stability in Crowded Environments* - Stepan Timr, Laboratoire de biochimie théorique, France
10:10 - 10:30	*Understanding biological data via MD: the hIFNγ glycosylation puzzle* - Nevena Ilieva, Institute of Mathematics and Informatics, Institute of Information and Communication Technologies at the Bulgarian Academy of Sciences (IICT-BAS), Bulgaria
10:30 - 10:50	**Coffee break**
10:50 - 11:30	*Molecular mechanism of RNA helicases* - Nicolas Leulliot, Cible Thérapeutique et Conception de Médicaments, Université de Paris, France
11:30 - 12:10	*Integrative approaches for modelling enzyme reaction-modulated assembly of phaseseparated biomolecular condensates* - S. Kashif Sadiq, Heidelberg Institute for Theoretical Studies, Germany
12:10 - 14:00	**Lunch**
14:00 - 14:20	*The complexity of signal transduction as elucidated by molecular dynamics* - Rachid Charbel Maroun, UMR-S U1204, INSERM/Université d'Evry-Val d'Essonne/Université Paris-Saclay, France
14:20 - 14:40	*The atomistic face of the human MHC-I peptide-loading complex* - Olivier Fisette, Center for theoretical chemistry, Ruhr-University Bochum, Germany
14:40 - 15:20	**Concluding discussions and future perspectives**
15:20 - 15:50	**Coffee break**

Oral contributions (in order of schedule)

Identification of protein functional regions

Francesca Nerattini [1], Matteo Figliuzzi [2], Luca Tubiana [1], Chiara Cardelli [1], Valentino Bianco [3], Ivan Coluzza * [4]

[1] University of Vienna – Austria
[2] Sorbonne Université – Sorbonne Université, UPMC, CNRS – France
[3] Complutense University of Madrid – Spain
[4] CIC biomaGUNE – Spain

Functional regions of proteins have evolved to have specific patterns of amino acids tailored to the activity of the biomolecule. The identification of the functional residues of such protein families was obtained with large scale mutation experiments where the effect on the protein function was tested against each alteration [1]. The information obtained with such experiments can have important implications for the mapping of the proteome interactions, as well as for many pharmaceutical applications, e.g. by identifying ligand-binding regions for targeted pharmaceutical protein design. However, the experimental determination of the functional regions is generally time-consuming and require extensive resources; hence a computational approach could help towards the final goal.

In this work, we propose an approach to identify functional regions of proteins to distinguish between residues that have a strictly functional role from the one that is important for the protein structural stability. The methodology that we propose here is based on the hypothesis that an artificial evolution process based on protein design, in the absence of any functional constraints, would lead only to co-evolution events of the structural type. Using Direct Coupling Analysis (DCA) [2], we identify conserved and co-evolved residues both in natural and artificial evolution processes. Just by subtracting the list of structural residues from the natural correlated and conserved ones, we show that we identify the functional residues.

References

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Keywords: PDZ, FKBP, and Response regulator

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*Speaker

Design of polymeric building blocks: Coarse graining, multiscale and theoretical predictions

Barbara Capone * [1]

[1] Roma Tre University – Italy

Creating novel building blocks, which allow for an easy and large-scale fabrication of complex materials, is a challenge and a central goal in material science. Much effort has been spent in creating tunable units that self-assemble into complex structures with particular features, and this has motivated an extensive analysis of functionalized building blocks of various shapes [1,2,3]. Polimeric systems have proven to be extremely functionaliable self-assembling building blocks with tunable properties [4]. A full atomistic description of such systems with atomistic potentials have proven to be extremely useful when describing the properties of a few particles, but when large scale simulations are required, it becomes essential to coarse-grain some degrees of freedom, while preserving all the underlying properties of the system. This talk focuses on the development and usage of multi-scale methodologies for polymers solutions, in particular on methods that allow to span from properties of single polymers, up to properties of dilute to semi-dilute solution of polymeric systems, with different architectures and chemical details. I will introduce and explain a coarse graining procedures that can, both theoretically and computationally allow to predict, and then represent properties of systems made by many microscopic units. I will show a few example of how such a methodology has been applied to systems of various chemical composition and physical architecture, and become a viable tool to design tunable building blocks whose mesoscopic self-assembly can be controlled by means of a few simple external parameters that can be accessed experimentally, as for example temperature, pressure, density or solvent quality.

References

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[4] Phys. Rev. Lett., 109, 238301, 2012.

Keywords: polymers, multiuscale, functionalised nanoparticles

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*Speaker

Simulating T=1 and T=3 capsid self-assembly

Dennis Rapaport [*] [1]

[1] Department of Physics, Bar-Ilan University – Israel

Viral capsids are known for their high symmetry and exquisite organization, but details of their assembly pathways are not readily accessible, neither theoretically nor experimentally. The nature of such nanoscale construction processes can, however, be explored by molecular dynamics simulations of simple rigid particles designed to form polyhedral shells, in particular the self-assembly of icosahedral shells from triangular particles, and shells corresponding to either T=1 or T=3 capsids from trapezoidal particles. These simulations reveal that under suitable conditions a high yield of complete shells can be obtained, and that successful assembly is attributable to a strongly reversible process which also avoids growth-inhibiting traps. Some aspects of the growth process appear universal, while others depend on particle shape and the size of the product shell. The inclusion of an explicit atomistic solvent proves to be an important element of the simulations. Insight gained from these simplified models has proved helpful in interpreting recent in-vitro experiments.

Keywords: virus, capsid, selfassembly, molecular dynamics

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[*]Speaker

Membrane shredding, poration, and fusion studied with molecular simulations

Ramachandra M Bhaskara [*][†] [1], Martin Vögele [1], Jürgen Köfinger [1], Gerhard Hummer[‡] [1]

[1] Max Planck Institute of Biophysics, Department of Theoretical Biophysics, Max-von Laue Str. 3, 60438 Frankfurt am Main – Germany

Biological systems need to actively shape, maintain and remodel cellular and organellar membranes to maintain homeostasis. Despite using advanced imaging methods, direct visualization of dynamic processes at biological membranes remains challenging. Molecular dynamics simulations provide us with a detailed view of how protein-bilayer interactions are translated into specific membrane shaping and remodeling functions. This talk will discuss how molecular modeling and simulations complement cryoEM and AFM experiments. Using large scale atomistic and coarse-grained simulations, we demonstrate (1) how the reticulon-homology domain of FAM134B assists selective ER-phagy by inducing and sensing membrane curvature, (2) how protein-lipid interactions of pneumolysin rings induce membrane-pore formation, (3) and how carbon nanotubes induce spontaneous vesicle fusion. Molecular simulations and modeling provide us with tools to study large-scale membrane-shaping processes and help us bridge the gap between theory and experiment.

References

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Keywords: Membrane remodeling, Pore formation, Fusion, Curvature, Sensing

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

Lars V. Bock [1], Michal Kolar [1], Andrea C. Vaiana [1], Andreas Russek [1], Helmut Grubmüller [*][†] [1]

[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.

References

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[*]Speaker
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Integrative, information-driven modelling of biomolecular complexes

Alexandre Bonvin [*] [1]

[1] Utrecht University - Faculty of Science (UU) – Netherlands

The prediction of the quaternary structure of biomolecular macromolecules is of paramount importance for fundamental understanding of cellular processes and drug design. In the era of integrative structural biology, one way of increasing the accuracy of modelling methods used to predict the structure of biomolecular complexes is to include as much experimental or predictive information as possible in the process.

We have developed for this purpose a versatile information-driven docking approach HADDOCK (http://haddock.science.uu.nl) [1,2]. HADDOCK can integrate information derived from biochemical, biophysical or bioinformatics methods to enhance sampling, scoring, or both [3]. The information that can be integrated is quite diverse with as most recent addition cryo-EM maps [4]. In my talk, I will illustrate HADDOCK's capabilities of integrating different types of experimental data with various examples and describe some recent developments around the modelling of membrane protein complexes and large assemblies. I will also introduce the concept of explorative modelling in which the interaction space defined by a limited number of restraints is systematically mapped [5].

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Keywords: Docking, interactions, assemblies, mass spectrometry, cryo, EM, NMR, bioinformatics, coarse graining, membrane

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[*]Speaker

Theoretical Characterization of Protein Folding Dynamics: Connecting Atomist Model with Time-Resolved Spectroscopy Data

Pietro Faccioli *† 1

1 University of Trento – Italy

From a theoretician's perspective, the characterization of the protein folding process involves overcoming three formidable challenges. First, one needs to generate a statistically significant ensemble of transition pathways, which provide extremely rare fluctuations. Next, the huge amount of data contained in the reactive trajectories needs to be reduced, in order to identify the essential slow processes and meta-states. Finally, theoretical predictions have to be validated against the existing experimental data, which typically provide information on the dynamics of a limited set of collective variables. In this talk we show how these three major steps can be undertaken by a specific combination of advanced enhanced sampling algorithms, statistical analysis and quantum chemical calculations, to provide contact with spectroscopic observables. We present applications to specific protein folding processes, where theoretical predictions are directly compared against time resolve linear spectroscopy data.

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Accurate calculation of protein folding energetics by difference

Javier Sancho * [1], Juan José Galano-Frutos [1]

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As proteins perform most cellular functions, quantitative understanding of protein energetics is required to gain control of biological phenomena. Accurate models of native proteins can be obtained experimentally but the lack of equally fine models of unfolded ensembles impedes the calculation of protein folding energetics from first principles. Here we show that an atomistic unfolded ensemble model, consisting on a few dozen conformations built from a protein sequence can be used in conjunction with an X-ray structure of its native state to calculate accurately by difference the changes in enthalpy and in heat capacity of the polypeptide upon folding. The calculation is done using Molecular Dynamics simulations and popular force fields and, for the two model proteins studied (barnase and SNase), the results agree within error or are very close to their experimentally determined properties.

Keywords: Protein stability, enthalpy calculation, heat capacity calculation, unfolded ensemble models, force field, water models, barnase, SNase

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*Speaker

Leveraging structural data by decoupling structure thermodynamics and dynamics

Frederic Cazals [*] [1]

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Decoupling structure, thermodynamics and dynamics to study the function of biomolecules allows leveraging specific structural data to focus on certain aspects. As a result, one typically obtain insights that might remain elusive for strategies applying a unique tool, say molecular dynamics, to study all aspects at once. In this talk, I will discuss several recent developments illustrating this perspective. In the first part, I will introduce a novel distance measure for conformations [1], as well as novel analysis shedding light on the multiscale structural conservation that may be present in conformational changes [2]. Applied to crystal structures of (homologous) proteins, these tools provide insights on dynamics without explicitly resorting to dynamics [3]. In the second part, I will argue that these insights may be used to stratify degrees of freedom (dof) i.e. internal coordinates into active / passive, and that the active ones may be exploited by basin hopping related methods to tame down the usual concentration phenomena in high dimensional conformational spaces. Novel methods to perform conformational exploration and analysis will be presented [4, 5, 6]. Finally, to bridge the gap to thermodynamics, I will introduce novel improvements to importance sampling / multi-phase Monte Carlo methods aiming at speeding up free energy calculations for (groups of) basins from the potential energy landscape [7]. Pointers to software tools implemented within the Structural Bioinformatics Library will be given [8].

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[*]Speaker

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Multiscale Simulation of Protein Assemblies

Gregory Voth [*][†] [1]

[1] Department of Chemistry, James Franck Institute, and Institute for Biophysical Dynamics, The University of Chicago, Chicago, IL, USA – United States

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. 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 large multi-protein complexes. Applications to experimentally important systems such as cytoskeleton actin filaments and HIV virions will be given.

Keywords: Ultra Coarse Grained, Coarse Grained, Beads, Biophysical Dynamics, Biomolecular, HIV, Cytoskeleton

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Molecular Transport Through Nanopores: Bridging Simulations and Experiment.

Igor Bodrenko [*][†] [1], Matteo Ceccarelli [2]

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[2] Department of Physics, University of Cagliari – Italy

Single-channel electrophysiology is a powerful technique to sense the interaction of single molecules with ion-conducting nanopores. The ion current through a nanopore incorporated into an artificial lipid membrane and induced by an applied potential is modulated by the substrate while entering, binding and leaving the channel. The ion current may be partially or completely blocked (so-called induced channel gating) during the time the substrate molecules stay inside the pore. The resulting substrate-induced ion-current fluctuations are the observable which contains the information on the pore-molecule kinetics. Besides, by using the reversal potential at concentration gradient conditions, one may estimate the permeability of charged molecules through the pore.

Typical time resolution in the electrophysiology allows one to reliably detect channel gating events longer than 10 μs. On the other hand, direct all-atom simulations of the system of few hundreds of thousand atoms (the pore, the membrane, the solute and the molecules of interest) can be used routinely these days to study non-equilibrium processes at up to the microsecond time scale. Thus, there is a gap of one order of magnitude, from 1 to 10 μs between the experimental and the theoretical capabilities to address the transport kinetics through nanopores. We will discuss recent advancements achieved in our group, in collaboration with experimentalists in order to bridge this time-scale gap from the both sides.

To quantify small molecule penetration into and eventually permeation through nanopores we applied an improved excess-noise analysis [1] of the ion current fluctuation caused by entering molecules. The kinetic parameters of substrate entry and leave are derived from a two-state Markov model analyzing the substrate concentration dependence of the average ion current, its variance and the power spectral density (PSD). Including filter corrections allows one to detect the kinetic rates constants far beyond the cutoff frequency of the instrumental ion-current filter and to extend the applicability of the electrophysiology to the diffusion time scale of few hundreds nanoseconds. From the simulation side, we will discuss two approaches. First, a multi-scale protocol includes the evaluation of the potential of pean force (PMF) of the substrate molecule in the pore and the local diffusion constants. The diffusion flux and, in principle, pore/substrate kinetic rates constants are calculated by solving the corresponding diffusion-drift equation [2]. The second method is the "from metadynamics to dynamics" approach [3]. The latter assumes location of the binding sites of the substrate in the pore and the corresponding saddle points using an enhanced sampling technique; evaluation of the average effective transition times in the metadynamics runs with subsequent scaling to the real transition times.

References

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Simulating nucleoprotein complexes: chromatin and ribosomes

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Chromatin architecture plays a key role in embryonic stem cell programming, human embryo development, brain function and cancer. Specifically, epigenetic methylation and acetylation marks are thought to control gene expression by dramatically altering global chromatin architecture; however, the exact mechanism by which a single methyl group can induce a large scale conformation change of chromatin is not well understood. By examining histones in a dense nucleosome context, our long term goal is to understand the electrostatics of this crowded environment. Using coarse grain models of chromatin as a basis, we construct all atom chromatin models and simulate these in explicit solvent with the GENESIS molecular dynamics code on the large-scale high performance platforms at Los Alamos National Laboratory. The multi-disciplinary effort combined computer science, high performance computing, chip design, biophysics, structural biology, and cell biology, including researchers from RIKEN, LANL, NYU, Intel and Cray. Several performance optimizations for the KNL architecture enabled scaling to large numbers of cores. Regarding the ribosome, we have used all-atom structure-based models to simulate tRNA accommodation, revealing alternative pathways for near- cognate tRNAs.

Keywords: RNA, molecular dynamics, coarse, grain model, nucleoprotein complexes

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Crowding in the cellular context: Tales of Clusters and Dynamics

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Biological macromolecules are highly concentrated in biological environments giving rise to crowding effects that impact structure, dynamics, and ultimately function. It is increasingly becoming clear that weakly attractive non-specific interactions may be a significant factor in crowding effects. Such interactions can lead to the dynamic formation of clusters which impacts diffusive properties and may lead to the formation of phase-separated states. Recent results from molecular dynamics computer simulations of cellular systems at different scales are presented that relate biomolecular interactions to cluster formation and altered diffusive behavior. Models of concentrated protein solutions, bacterial cytoplasms, with and without the presence of membrane surfaces are discussed. The models range from fully atomistic systems to coarse-grained models derived from the atomistic systems in order to expand to larger spatiotemporal scales. Where possible, the results from the simulations are related to experimental data.

Keywords: crowding, molecular dynamics, coarse, grain models

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Predicting the structure of RBP recognition elements

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Improvements in genomics give us access to an unprecedented amount of RNA sequence data, coding and non-coding. It is a general desire to determine the structure and function of these RNAs in order to discover: binding sites to proteins, DNA, other RNAs, and small molecules; search in transcriptomic and genomic data for sequences with similar structure and function; and, design new sequences with predetermined properties. The success of accomplishing these tasks depends on the representation of an RNA sequence that we use. Here, I will introduce a new representation based on a feature vector that is appropriate to machine learning, which we are using to identify overrepresented structural motifs from RNA folding prediction data . Interestingly, the overrepresented motifs are determinants of RNA function. From this representation, we derive decision-tree based RNA family classifiers, and show that mutations that affect the outcome of these trees also affect function. Finally, we use it to model and search for the structure of RNA-binding protein recognition elements.

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BZip transcription factors modulate DNA supercoiling transitions – potential transcription regulatory mechanism: insights from molecular modelling

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Torsional stress on DNA, introduced by molecular motors when the molecule undergoes under- or overtwisting, constitutes an important regulatory mechanism of gene expression [1].Torsional stress can modulate specific binding of transcription factors to DNA, introduce local conformational changes that facilitate opening of promoters and nucleosome remodelling [1,2]. Using all-atom microsecond scale molecular dynamics simulations together with a torsional restrain [3,4] that controls the total helical twist of a DNA fragment, we study the impact of torsional stress on MafB-DNA complexation. MafB (PDB ID: 4AUW)[5] is a representative of human bZIP family of transcription factors, which recognizes the palindromic DNA sequence (TGCTGACGTCAGCA). We over- and underwind free DNA and DNA in complex with MafB by 5○ per dinucleotide step, and monitor the evolution of the protein-DNA contacts at different degrees of torsional stress. Our computations show that MafB changes the DNA sequence-specific response to the torsional stress; the dinucleotide steps that are anticipated to absorb most of the stress become more torsionally rigid as these are involved in the specific protein-DNA contacts. Also, the protein undergoes substantial conformational changes to follow the DNA deformation and maintain, at all times, the specific contacts with DNA. This results in an asymmetric increase of the free energy cost of twisting molecular transition, with respect to fee DNA, where overtwisting is significantly energetically unfavorable. Our data suggest that MafB could act as a "torsional stress insulator" creating a suitable topological environment that can, among all, promote cooperative binding of other TFs.

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Keywords: DNA, molecular dynamics simualtions

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MD simulation combined to fragment based approach for protein-peptide complex structure prediction

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Protein-protein interactions play a key role in almost all cellular functions. The modulation of these interactions has many therapeutic applications, but the physical characteristics of these interfaces make the rational design of inhibitors difficult. The rational design of peptide inhibitors is an explored strategy for modulating protein-protein interactions. Numerical prediction of the binding modes and affinity of a peptide on a protein presents many difficulties. We use molecular dynamics simulations of protein in the presence of small peptides to identify binding sites and key *hot-spots*. Binding affinity of small peptides being weak, these simulations intend to sample extensively peptide binding around a target protein. Out method has been tested on a set of nine proteins-peptide complexes which structure have been solved in free and complexed forms. In all case we were able to identify at least one binding site overlapping with the crystal peptide binding site. Different metrics have been used to characterize each binding sites and in particular their peptide sequence specificity and affinity. The proposed method aims a better prediction of peptide protein structure prediction and ultimately to optimize the peptide sequence or predict de novo optimal peptide composition.

Keywords: Protein Peptide interactions, MD simulation

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Degeneracy in Molecular Scale Organization of Biological membranes

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From lipidomics research, it is now known that there are more that 40,000 lipid structures in Eukaryotic cells and the plasma membrane itself has more than 800 different types of lipids. Differential molecular interactions among these extremely diverse constituents give rise to spatiotemporal heterogeneities in the membrane structure. These sub-100 nm transient sub-structures, which are generally stabilized far away from equilibrium in cells, are believed to be functionally important in various physiological processes. One of the fundamental questions in the field is "Why are there so many lipids?"

In this work, we explore the molecular origin of the variety in membrane organization using tools from simple statistical mechanics theories. We use a lattice model for the lipid mixtures, where the lattice Hamiltonian is trained from long microseconds all-atom (AA) simulations [1,2] on lipid bilayer systems that exhibit ordered and disordered fluid phase co-existence. Using stochastic optimization process of Monte Carlo simulated annealing, we evolve the Hamiltonian for lateral organization and show that model membrane with "realistic" lipid constituents show the ability to form a large range of membrane substructure space (higher degeneracy and complexity) as compared to "in-vitro" lipids, which form only one kind of substructure even with changing composition. We show that the disconnectivity graph [3] of the potential energy landscape for "in-vitro" systems have distinct funnel energy landscape, while physiologically relevant systems have a more frustrated glass-like energy landscape, which are capable of higher functional diversity due to their ability to form multiple degenerate membrane sub-structures.

Experimental results on membrane dynamics from super resolution techniques and single particle tracking diffusion measurements [4,5] have indicated that smaller domains with highly complex morphologies, resulting from non-ideal mixing of membrane constituents, are observed in both lipids only systems and lipids-proteins bilayer systems. The new non-affine displacement-based framework to characterize lipid order and disorder at nanoscale (with surface diffusion data) could be useful in interpreting data from super high resolution tracking experiments that exhibit highly complex dynamical behavior of lipids in the crowded in-vivo membrane environments.

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Focusing the Computational Microscope on Bacterial Cell Envelopes.

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The cell envelopes the protect Gram-negative bacteria are complex, multicompartment molecular architectures. But in order to defeat harmful, disease-causing bacteria it is imperative that we unravel the structure-dynamics mysteries of these cell envelopes. To this end we have developed atomistic-level models of the two membranes and cell wall that constitute the cell envelope of *E. coli*. Our simulations have begun to provide some insights into the dynamic interplay between the different components and the structural consequences of these dynamics. At a more coarse-grain level, we have recently started looking at how outer membrane vesicles, which are shed by all bacterial studied to date, interact with model plasma membranes. Our large simulations of systems of millions of particles are beginning to provide insights into steps that are important in the process of infection. I will discuss both the atomistic and coarse-grain strands of our work in this presentation.

Keywords: modelling, coarse, grain

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Reweighted-Probability Enhanced Sampling: a reversed perspective on metadynamics

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One of the areas of atomistic simulations that has received more attention in the past years is enhanced sampling. Especially when dealing with biological systems, present computers fall short of what would be needed to simulate phenomena that in the lab take place on macroscopic timescales. Thus a plethora of different methods have been suggested to overcome this difficulty. Among them, metadynamics has become rather popular in recent years, and with it the idea of building an on-the-fly bias potential capable of adjust itself to the characteristics of the system. This kind of approach has been used not only for exploring phase space or calculating free energies, but also to fit coarse-graining models and to directly enforce knowledge coming from experiments, in order to compensate for the limitations of molecular dynamics force fields. We believe that the two areas are deeply connected and that any improvement in enhanced sampling has the potential to bring new insight to coarse-graining or simulations-experiment bridging. We propose here a novel perspective on metadynamics which, by shifting the focus from the bias potential to the sampled probability distribution, allows for a much improved convergence rate, and opens up to new possibilities. In particular the new algorithm can greatly outperform standard metadynamics when dealing with suboptimal collective variables, thus in the case some slow degree of freedom is missing in the reduced description of the system.

Keywords: enhanced sampling, metadynamics, free energy, methods

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*Speaker

Combining computational and experimental approaches to comprehend the "how" and "why" of bacterial transcriptional regulation

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Recent advances in high-throughput sequencing technology have yielded a huge increase in our knowledge of genomic sequences, but DNA sequence information remains meaningless without corresponding functional insight. It is only through a synthesis of computational approaches and highthroughput experiments that any meaningful headway can be made in the task of moving from genome sequence information to functional information at the scales of modern biology.We have recently launched two such initiatives, aimed at completely mapping the transcriptional regulatory logic and functional proteome of Escherichia coli. Using a broadly applicable non-specific method for mapping genome-wide protein occupancy, we have begun to identify the binding motifs, functions, and condition-dependent behavior of many cryptic E. coli transcription factors. In the process, we have also identified the presence of heterochromatin-like silenced regions on bacterial chromosomes, which we have found play a key role in regulating stress-response and virulence genes across several bacterial species. Combination of our findings with multiscale simulations of protein-DNA interactions promise to provide a unifying model for the interplay of bacterial chromosomal structure and gene expression. To address the problem of assigning functions to poorly annotated proteins without suitably close homologs for sequence-based annotation methods to be effective, we have recently developed a hybrid pipeline combining structural prediction/alignment, sequence alignment, and protein-protein interaction information to obtain combined structure predictions and functional annotations for entire proteomes. We find that our inclusion of structural information makes our workflow unusually strong in performance on difficult targets with limited sequence identity to annotated proteins. Application of our methods at the scale of entire proteomes yields a rich new source of information to seed detailed investigation of the functions of many previously mysterious protein-coding genes.

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Understanding the interplay between RNA molecular flexibility, structure and chemical probing using all-atom molecular dynamics simulations

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Ribonucleic acid (RNA) molecules are involved in most steps of the genetic expression including catalysis of central cellular functions. RNA function depends crucially on the specific tridimensional folding of the molecule which in turns depends on the sequence and on the way the bases pair through hydrogen bonds (secondary structure). Hence, determination of RNA tridimensional structures is fundamental for understanding their function. A common method to investigate RNA structures of large molecules is the use of chemical probes such as SHAPE (2'-hydroxyl acylation analyzed by primer extension) reagents, DMS (dimethyl sulfate) and CMCT (1-cyclohexyl- 3-(2-morpholinoethyl) carbodiimide metho-p-toluene sulfate), the reaction of which is dependent on the local structural properties of each nucleotide. In order to understand the interplay between local flexibility, sugar pucker, canonical pairing and chemical reactivity of the probes, we performed all-atom molecular dynamics simulations on a set of RNA molecules for which both tridimensional structure and chemical probing data are available and we analyzed the correlations between geometrical parameters and the chemical reactivity. Our study confirms that SHAPE reactivity is guided by the local flexibility of the different chemical moieties but suggests that a combination of multiple parameters is needed to better understand the implications of the reactivity at the molecular level. This is also the case for DMS and CMCT for which the reactivity appears to be more complex than commonly accepted.

Keywords: RNA, chemical probing, molecular modelling, flexibility

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[*]Speaker

Multifunnel energy landscapes - how multiple functions are encoded in biomolecules

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Exploration of the energy landscape of biomolecules gives access to all information necessary to calculate structural, mechanistic, thermodynamic and kinetic data. Discrete path sampling (DPS) has been developed to utilise geometry optimisation techniques to allow for efficiently sampling energy landscapes. In this talk I will discuss the recent application of DPS to multifunctional biomolecules. The discussion will include case studies, a descriptions of charachteristic topologies, and implications of our results for experiments and biomolecular design.

Keywords: Multifunctional biomolecules, Multifunnel energy landscapes

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*Speaker

Multiscale modelling of RNA and DNA structural motifs

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Natural and artificial RNA structures could be understood as assemblies of recurrent building blocks - the structural motifs. Non-helical motifs often play a key role. These include internal loops such as C-loops or kink-turns, terminal loops, or junctions where three or more helices meet. In the DNA world, non-helical motifs such as the DX motif serve as helix connectors in nanostructures. We set out to model these motifs at various levels of detail. To this end we adopt a consistent bottom-up approach where large-scale atomistic MD simulations with explicit inclusion of water and ions are a source of data to parametrize models with reduced number of degrees of freedom. We employ models where bases or base pairs are considered rigid objects, and those where groups of bases are represented as effective rigid bodies. The coarse-grained coordinates are computed for each snapshot of the atomistic MD trajectory, resulting in a statistical ensemble from which the model paramers describing its structure and stiffness are deduced. In this way, the mechanical properties of the motif as a whole are captured, which enables one to assemble the motifs into larger structures inaccessible to atomistic simulations.

Keywords: RNA, DNA, structural motifs, molecular dynamics, coarse, grained models, mechanical properties

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Exploring RNA flexibility through a coarse-grained model and its coupling to experimental data

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Thanks to the multitude of possible base pairings, RNA molecules are systems capable of adopting different three dimensional structures in response to the environment. Recent studies have shown how their energy landscape is characterized by the presence of several funnels, making their behavior depart from the simple paradigm of a "folding funnel" that has been successfully applied to globular proteins. The study of the folding and of the large conformational transformations of RNA molecules is therefore essential to understand their interplay in the cell. Atomistic studies are limited in this respect as they can only observe relatively local transformations, the typical size of the systems being too big to address more large-scale questions. The HiRE-RNA coarse-grained model has been developed in recent years to overcome the limitations of atomistic descriptions and to complement them. Its aim is the study the large scale rearrangements of non coding RNAs, to predict folding at least for small systems, to study the interconversions between alternative structures and assembly. In this presentation I will present the basic elements of the model together with the most significant applications showing how it is suited to the study of alternative conformations and rugged landscapes. Given the multitude of possible stable structures for a given sequence, the importance of the environment for the structure that the system adopts in a specific circumstance becomes key. Even with the best modeling tools available, the information coming experiments is essential to understand what particular structure is adopted, and the coupling between models and experiments is more relevant than ever. I will discuss how coarse-grained modeling is particularly apt at incorporating data from experiments and experimental conditions and present our work in progress on how to couple HiRE-RNA to experiments. In particular I will focus on how to incorporate local constraints such as base-paring, the recent developments on how to account for pH, the basis on how to incorporate SAXS data, possible strategies to account for chemical probing and I will present interactive simulations, giving the chance to the user to directly stir the simulation to explore specific structures.

Keywords: RNA, coarse, grain, HiRE, RNA, SAXS, pH

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Exploring macromolecular machine mechanisms with numerical tools

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When powered by nucleotide hydrolysis, self-assembled homo-oligomeric complexes can undergo concerted motions that generate mechanical movements of their binding partners. Such mechanisms are notably commonly used to dissociate, translocate or condensate nucleic acid strands. They result from the interplay between atomic level interactions and global assembly organization, over different time-scales. Most often, homo-oligomeric dynamic systems escape experimental characterization, notably due to symmetry breaking. Numerical approaches can then help deciphering the mechanism. I will discuss known cases of cyclic assemblies where coexistence of different interfaces within a same ring-shaped oligomer was associated to sequential stages in the hydrolysis process and I will present how this type of mechanism may apply to so-called collaborative filaments [1] such as the homologous recombination filaments. Our investigations combining coarse-grained docking and high-resolution molecular dynamics simulations indicate the possibility of a weaving-like mechanism that would explain why ATP hydrolysis destabilizes the products of homologous recombination [2].

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Keywords: coarse, grained, docking, molecular dynamics simulations

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Improving the performance of the RNA AMBER force field by tuning hydrogen bonding interactions

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I will introduce our efforts to improve the pair-additive AMBER force field (ff) for RNA. I will explain the limits of the currently used ff form, which we try to circumvent by adding a new simple ff term for tuning of H-bonding called gHBfix. gHBfix is orthogonal to the basic ff terms and can thus improve the simulation performance without causing undesired side effects. I will show that several recently published RNA ff versions have been over-fitted to A-form RNA (based on NMR data on RNA tetranucleotides) and are not suitable for simulations of folded RNAs. Then I will briefly describe our efforts to use MD simulations to capture structural dynamics and partial disorder at protein-RNA interfaces, extending the picture provided by ensemble-averaging experimental methods. Structural dynamics may allow the proteins to read simultaneously multiple RNA targets, to scan the RNA chain, and to de-couple affinity of binding from catalytic activity via transiently populated but highly reactive conformations. Finally, I will briefly comment on limitations of collective-variable-based enhance-sampling methods to capture the essence of folding of DNA quadruplex molecules.

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[*]Speaker

Possibilities and current limitations of joining MD simulations and experiments: the cases of amyloid aggregation and membrane binding proteins

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In this talk I will show for two different examples how the combination of molecular dynamics (MD) simulations and experiments enrich each other, thereby providing a more complete picture of the dynamics and interactions of proteins than the sole application of each of the individual methods would reveal. The first example is concerned with protein aggregation, which is the main area of interest in our group. The aim of our work is to understand the physicochemical principles that govern the highly complex process, which may lead to fatal diseases, as in the case of Alzheimer's disease. All-atom molecular dynamics (MD) simulations of protein aggregation in explicit solvent have been performed for over a decade, revealing valuable information about this phenomenon. However, these simulations are challenged by three main problems: (1) The accuracy of current all-atom force fields in modeling protein aggregation is insufficient.[1] We currently work on first identifying why the force fields fail to reproduce the aggregation kinetics and then resolving these problems. (2) The second problem is that all-atom MD simulations of protein aggregation are generally performed at protein concentrations orders of magnitude higher than the comparable in vitro and in vivo situations, limiting structural rearrangements between aggregate growth events.[2] In order to overcome this limitation much longer simulations of the individual aggregation states are needed than was done in the past, as we showed in our recent work.[3] (3) The third problem is the well-known length- and time-scale problem. Even when we manage to simulate the aggregation process for tens or even hundreds of mircoseconds, this is not enough to meet the corresponding scales usually tested in experiments of protein aggregation, which report on nm-to-μm long aggregates that form on the time scale of minutes and beyond. This limitation can only be solved by designing experiments that also report on the early aggregation events, and by developing multiscale simulation approaches that will allow to extend the length- and time-scales to be simulated. Similar problems are also faced in the second example that I will discuss in my talk, which is about the aggregation and lipid-membrane binding of guanylate binding proteins.

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*Speaker

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Getting divalent ion–biomolecule interactions right in Molecular Dynamics simulations

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Ion-biomolecule interactions are ubiquitous and play a central role in a number of fundamental biological processes, from calcium signaling to the formation of DNA–protein complexes. Molecular level understanding of these key biological processes first requires to characterize the interaction between biomolecules (proteins and nucleic acids) and divalent cations, which is both an experimental and computational challenge. Indeed, standard biomolecular simulations using non-polarizable force fields suffer from severe overbinding artifacts-especially with divalent cations like Ca 2+ and Mg 2+ -that prevent them to properly capture ion-biomolecule interactions. We aim to improve the description of divalent cations in simulations and use it to tackle biologically relevant problems. Our strategy is to start with small model systems, where simulation results can be directly compared both to experimental data (e.g. neutron scattering, capillary electrophoresis, etc.) and to reference high-level ab initio simulations in order to systematically assess the validity of our descriptions. These results are used to develop a scaled charge description of the ions and charged biomolecular groups, which takes into account electronic polarization in a mean field way. Such a description has been shown to successfully improve ion-binding properties in different biosystems. This new original method opens the way to large-scale, accurate, and computationally cheap simulations of divalent cation containing biosystems. Future plans are to use it to improve our molecular understanding of the impact of ions on nucleic acid structure and reactivity.

Keywords: molecular modeling, ions, proteins, nucleic acids

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[*]Speaker

Combining diverse information and techniques to understand biological function

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Biological systems pose many challenges for researchers. The relevant timescales span more than 9 orders of magnitude, and even for bacteria the relevant length scales span 6 orders of magnitude. Many tools offer excellent information within a limited range of time and length. For example, molecular dynamics simulations have provided enormous insight into protein function; however, the time and length scales of the results is limited. Crystallography offers a power tool, but many important functions of proteins are governed by regions that are usually unstructured. Such regions are not readily probed using crystallographic methods. Single molecule measurements have provided many unexpected new results, but great care must be taken in relating those results to in vivo systems.

For more than half a century, physicists have studied general features of biological systems to try to find governing principles that apply to a range of situations. For example, many theorists considered how the search for a particular position in a long linear target. Sequence dependent proteins seeking particular sequences along a bacterial chromosome provide an example of such a search. The physicists showed that optimal searches combine the following: 1. One dimensional "diffusion" long the target 2. Short hops between sites that separated by slightly longer than the typical diffusion length 3. Large jumps between sites that have large separations along the linear target, though they may be physically close if the target is looped. Knowing this general strategy helps people consider how particular proteins behave, but it does not explain how the "diffusion occurs", or when and how the searcher makes the transition between searching modes. Similarly, John Hopfield suggested that biological systems can provide arbitrarily good discrimination between binding sites whose energies are very similar, if the biological system uses kinetic proofreading; however, the time required to establish the correct binding increases as the requirement for discrimination increases. This is a special case of the more general speed/stability paradox, which our group has extended to the speed/stability/stringency paradox.

Our group has combined single molecule experiments, general physics modeling of systems, statistical studies of the sequences of bacterial genomes, and molecular dynamics simulations done in collaboration with the Prévost group to elucidate how double strand break repair in bacteria progresses if it follows the RecBCD pathway. The details of that process will be presented, along with information on general strategies that we learned from studying this system. Interestingly, the overall strategy is similar to that pursued by humans seeking the perfect mate. Insights from this system may also help cast light on protein folding and other self-assembly processes in which the correct structure represents a very small minority of all possible structures.

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A Native Molecular View of Cells by Cryo-ET - Structural Biology Done In-Situ

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In situ cryo-electron tomography - i.e. cryo-focused ion beam (FIB) milling in conjunction with cryo-electron tomography (cryo-ET) - has changed the way biological systems can be analyzed and modeled. Using this approach, intact cells can now be imaged in a native state and at high resolution, allowing both the quantitative analysis of cellular constituents (visual proteomics) as well as modeling of dynamic cellular processes. Some of these processes might be rare (1-2 events per cell), or localized to specific sites within a cell (e.g. endoplasmatic reticulum, cell membrane, etc.) and therefore need to be specifically targeted, to not be missed during the milling process. We therefore use a 3D-correlative approach, combining confocal cryo-fluorescence microscopy (FLM) and FIB milling to study such rare biological events.

In our research, we address how ribosomes are formed in a variety of organisms. For eukaryotic cells - including the unicellular green alga Chlamydomonas reinhardtii - ribosome precursors are produced in the nucleolus, where essential processing steps take place, before the individual precursors are exported to the cytoplasm where they are assembled and mature into a fully functioning ribosome. Using cryo-FIB milling together with template matching and subtomogram averaging, we were able to dissect the organization of this non-membrane-bounded organelle, and shed light on the molecular details of ribosome biogenesis in C. reinhardtii. We here present the first in situ averages of its small subunit (SSU) as well of its large subunit (LSU) precursor, the pre90S and pre60S particles respectively. We use advanced classification techniques to ensure we only keep true positives during subtomogram averaging. This has allowed us to clearly discriminate between distinct states of ribosome precursor maturation as well as their native spatial organization within the nucleolus.

In addition to ribosome biogenesis, we also apply triad of cryo-FLM, cryo-FIB and cryo-ET to address open questions in the field of autophagy, namely clearing of aberrant endocytic events. Autophagy (or more specifically macro-autophagy) is an essential process for protein homeostasis inside cells. Structures that are damaged, or no longer needed can be directed toward degradation via sequestration into a double-membrane structure, the autophagosome, which later fuses with the lysosome or the vacuole to submit its payload for degradation. Cargo specificity can be realized though means of receptors, which bind to particular cellular structures and thus target them to the autophagosomes. We have identified a new type of receptor, an ?intrinsic receptor?, which on one hand is involved in a specific cellular process (endocytosis), but which in itself can also act as a receptor for autophagy if said cellular process becomes abnormal. We apply 3D-correlated cryo-light and electron microscopy to study this receptor and its effect on the autophagic machinery to reveal the early stages of clearing aberrant endocytic events on a molecular resolution level.

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Towards a holistic view of DNA

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DNA is a paradigm of a multiscale system. The study of DNA means to analyze at the simultaneously sub-Angstrom details and a meter-long fibre. Multiphysic approaches, combining different techniques need to be developed and used. I will summarize during my talk recent advances done in Barcelona on the multi-resolution description of DNA, giving examples on the type of information on DNA that can be extracted from such theoretical methods

Keywords: Modelling, DNA

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Multi-Scale Simulations Yield Insight into Protein Diffusion and Stability in Crowded Environments

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Proteins inside the living cell are exposed to a highly crowded and heterogeneous environment, which may substantially affect their properties and, consequently, their function. Recent experimental evidence indicates that both the diffusivity and the stability of a protein can be altered by tuning its interactions with the crowded environment. To gain a detailed understanding of these effects, microscopic insights from molecular simulations are strongly desired; however, the wide spread of the time- and length scales involved in macromolecular crowding poses a significant challenge for conventional simulation approaches. Here we combine lattice Boltzmann molecular dynamics with all-atom replica exchange simulations into a computational framework that allows us to investigate protein diffusion and stability in crowded solutions. We employ our computational scheme to examine how the stability of a protein is modulated by distinct states of local packing occurring in the crowded solution. Furthermore, we show how our molecular simulations allow rationalizing the results of fast relaxation imaging (FReI) measurements of protein stability in crowded conditions.

Keywords: multiscale simulations, molecular dynamics, macromolecular crowding, protein diffusion, protein stability

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Understanding biological data via MD: the hIFNγ glycosylation puzzle

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Human interferon-gamma (hIFNγ) is a key immunomodulating secretory glycoprotein. The biologically active form of the cytokine represents a non- covalent homodimer, each of the monomers being 143 aa residues long. The natural cytokine is a glycoprotein with two N-glycosylation sites in each monomer chain – Asn25 and Asn97, which are independently and differentially glycosylated. Although glycosylation is not necessary for its activity, it does affect the physico-chemical properties of the cytokine. There is experimental evidence that glycosylation promotes the folding and dimerization of the recombinant protein and also protects hIFNγ from proteolytic degradation, thus extending its circulatory half-life.

Recently, it was found that when labeled with His6-FLAG tag added to their N-termini, both glycosylated (expressed in insect cells) and non- glycosylated (expressed in E. Coli) forms of the fusion protein exhibit 100 times lower that expected biological activity. Upon removal of His6-FLAG tag the non-glycosylated forms recover their activity, while in the glycoforms the tag becomes enterokinase-resistant and cannot be removed.

We present a MD study on human hIFNγ to shed light on the mechanism through which glycosylation preserves the integrity of the cytokine molecule. We report the development of several in silico models of glycosylated native hIFNγ fusion proteins. By means of long-scale MD simulations we reveal the restrictive role of the glycans for the wagging motion of the highly volatile C-termini by keeping them within a reduced ensemble of conformations closer to the globular part of the cytokine. That way, the functionally important sequences in the globule are preserved from protease attacks in the blood flow. At the same time, sporadic individual contacts between the gly- cans and the C-termini allow the proteolysis of the last several amino acids that yields more stable and biologically active forms of the cytokine with different truncation grades. Thus, we are faced with a double-sided mecha- nism of glycosylation-governed activity modulation by decreasing the entropy of the initial state (responsible for the stabilisation of the hINFγ molecule and prolongation of its circulatory half-life, at typical activity levels) and by increasing the enthalpy of the final state (related to the appearance of differently truncated forms, some of them with a higher biological activity). Ultimately, both are favorable for the biological function of the cytokine, so glycosylation is indeed the key to the stability and the preserved high activity of hIFNγ. The above findings are presented in two recent papers:

- E. Lilkova, N. Ilieva, P. Petkov, E. Krachmarova, G. Nacheva, and L. Litov Molecular dynamics simulations of His6-FLAG-hIFNγ fusion glycopro- teins accepted in: I. Georgiev et al. (eds.) Advanced Computing in In- dustrial Mathematics, Studies in Computational Intelligence (Springer Nature Switzerland AG, 2020?)

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- E. Lilkova, P. Petkov, N. Ilieva, E. Krachmarova, G. Nacheva and L. Litov Molecular modeling of the effects of glycosylation on the structure and dynamics of human interferon-gamma J. Mol. Modeling (2019); DOI: 10.1007/s00894-019-4013-8.

Keywords: molecular modeling, molecular dynamics, human interferon, gamma, glycosylation, glycoprotein models, high resolution methods

Molecular mechanism of RNA helicases

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RNA helicases are often compared to a nanoscale motor that can translocate along the RNA, dissociating bound RNA and/or proteins to allow structural rearrangements in protein-RNA complexes. In the DEAH-box RNA helicase family, Prp43 is a remarquable bifunctional enzyme, required both for ribosome biogenesis and splicing, and activated by G-patch domain-containing proteins. The molecular mechanisms governing how Prp43 is activated by its G-patch protein partners remain poorly understood, as is the function of all helicases of the other DEAH box helicase family involved in splicing and ribosome biogenesis. We have investigated if the G-patch protein activation was linked to the unique nucleotide binding mode of this helicase family. Using magnetic tweezers on a model system, we have for the first time observed the activity of yeast DEAH proteins at the single molecular level. We show that given a G-patch protein co-factor, all the helicases are able to processivily unwind short stretches of nucleic acid duplexes in repetitive unwinding and reannealing cycles. We propose a unifying structural and functional model for DEAH helicase mechanism, activation and function in large macromolecular complexes. In this model, DEAH box helicases appear as motors in neutral gear, and interaction with G-patch domain proteins engages different gears to provide the helicase different speeds and/or processivity. Our understanding of the molecular mechanism governing DEAH helicase function and activation remains limited.

Keywords: RNA helicases

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Integrative approaches for modelling enzyme reaction-modulated assembly of phaseseparated biomolecular condensates

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Computational molecular modelling techniques provide a route to integrate existing experimental techniques into a predictive spatiotemporal picture of molecular biology. But important challenges remain to account for the multiple scales involved. Here, I will present several integrative methods that we are developing that aim to bridge these spatiotemporal scales.

I will firstly discuss methods we are developing that couple high-throughput allatom molecular dynamics (MD), Markov state models and Brownian dynamics (BD) simulations to predict the kinetics of conformation-gated slow ligand-binding processes. Furthermore, by combining MD with solution NMR techniques, I will show how we optimally fit spectra and thus identify experimentally validated transitions between relevant conformational ensembles beyond the timescale-reach of MD alone. Focusing on the process of HIV-1 virion maturation and infectivity, I will then discuss how ultra-coarse-grained interaction particle-based reaction diffusion (iPRD) models can be employed to investigate biochemical spatiotemporal reaction networks in the context of crowding, molecular diffusion and macromolecular architecture – guided by experimental data from cryo-EM and super-resolution microscopy techniques.

Finally, I will discuss how we combine modelling methods with AFM and enzymatic assays to probe the condensate behaviour and molecular function of the HIV-1 ribonucleoprotein, an example of a phase-separated membrane-less granule that contains self-assembled RNAprotein mixtures - especially with a view to understanding generally how enzyme reactions in such granules might be modulated and specifically to provide insight into the corresponding biological function in the case of virion maturation.

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The complexity of signal transduction as elucidated by molecular dynamics

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In this work, we study the mechanisms of activation and inactivation of signal transduction by the histamine H3 receptor (H3R), a 7TM GPCR through extended molecular dynamics (MD) simulations of the receptor embedded in a hydrated double layer of dipalmitoyl phosphatidyl choline (DPPC), a zwitterionic poly-saturated ordered lipid. Three systems were prepared: the apo H3R, representing the constitutively active receptor; and the holo-systems: the H3R coupled to an antagonist/inverse agonist (ciproxifan) and representing the inactive state of the receptor; and the H3R coupled to the endogenous agonist histamine and representing the active state of the receptor. An extensive structural and dynamical analysis of the MD simulation trajectories shows that the three states of H3R present important structural and dynamic differences in several geometric and energy properties and that the behavior of this system is complex given that the measured properties interact in multiple and inter-dependent ways. For instance, rotamer toggle switches involved in the mechanism are multiple and not just single nor double, as reported before. In addition, the MD simulations describe an unexpected escape of histamine from the binding site, in agreement with the experimental rapid off-rates of agonists.

Keywords: 7TM receptors, GPCR, signal transduction, histamine H3 receptor, molecular dynamics

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[*]Speaker

The atomistic face of the human MHC-I peptide-loading complex

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Antigens exposed at the cell surface by major histocompatibility complex class I (MHC-I) proteins enable self/non-self recognition by cytotoxic T cells, protecting the organism against viral infections and cancer-causing mutations. To perform their role, MHC-I must first be loaded with an antigenic peptide in the peptide-loading complex (PLC), a large multi-protein assembly whose atomic-level structure and dynamics are still poorly understood.

Using all-atom molecular dynamics (MD) simulations, we studied key elements of the human PLC, how they stabilise MHC-I and catalyse antigen selection, and how they assemble to form the PLC. By combining microsecond-timescale MD simulations with a recent 6-Å-resolution cryo-EM structure of the PLC, we obtained an atomistic model of the complete complex, in explicit solvent and in a membrane environment (1.5 million atoms). This model offers unprecedented insights into the structure and dynamics of the human antigen-loading machinery.

Our simulations explain how tapasin, a central component of the PLC, acts as both an MHC-I chaperone and a catalyst that accelerates the off-rate of low-affinity peptides to facilitate antigen triage (peptide editing). We also show how tapasin recruits the transporter associated with antigen processing (TAP) into the PLC via transmembrane interactions. Finally, truncating antigens or removing them from the MHC-I binding groove gives a spatially resolved map of MHC-I plasticity which reveals how peptide loading status affects key structural regions.

Taken together, our MD simulations explain experimental kinetics and mutagenesis data, and represent the first in-depth, atomic-level study of the mechanisms underlying the biological function of the PLC, an important step towards a better understanding of adaptive immunity.

Keywords: MD simulations, cryoEM, MHCI, PLC

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Posters

Poster 01

Partial Dissociation of Antigenic Peptides from MHC I – Linking NMR Data to Microstates Observed in MD Simulations

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Major Histocompatibility Complex I (MHC I) is one of the key players in adaptive immunity. Expressed on the surface of all nucleated cells, it displays sample antigenic peptides from the cytosol to patrolling cytotoxic T-cells that can thus identify and kill malignantly transformed and virally infected cells.

Although several crystal structures of MHC I in complex with an antigenic peptide (pMHC I) have been solved, the structural dynamics of pMHC I at the cell surface remain largely elusive. According to a recent NMR study on HLA-B*35:01 (Yanaka et al., J. Biol. Chem., 2014), pMHC I complexes can adopt a minor state in which the antigenic peptide is bound tightly to MHC I and a major state in which the peptide is bound more loosely. In unbiased MD simulations of the pMHC I studied by Yanaka et al., the peptide N-terminus dissociated from the MHC I binding groove during a few hundred nanoseconds. This finding suggests that pMHC I with completely bound peptide may correspond to the proposed minor state, whereas pMHC I with partially dissociated peptide may constitute the major state.

To underpin this, the potential of mean force (PMF) along the distance between the anchor residue of the peptide N-terminus and its binding partner in the MHC I binding groove has been calculated. The resulting free energy differences can be compared to values derived from the published NMR data. Preliminary results from umbrella sampling (1 microsecond of MD simulation per umbrella window) suggest that pMHC I in which the peptide N-terminus has dissociated from MHC I are lowest in free energy. Contrarily, Hamiltonian replica exchange simulations (2 x 2 microseconds), in which the effective temperature of the MHC I binding groove and the antigenic peptide is increased, predict pMHC I with completely bound peptide to be the global minimum of the free energy. This seemingly contradicting difference is discussed and further elucidated.

Keywords: Major Histocompatibility Complex I (MHC I), molecular dynamics (MD), enhanced sampling, umbrella sampling, replica exchange

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Poster 02

Augmented Reality and Virtual Reality tools for visualization of Molecular Dynamics simulations

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The design of new advances in the field of computational simulations and visualization tools provide new opportunities to optimize the design of supramolecular entities at structural level. Different examples carried out recently in our research group will be presented, such as the development of a mapping algorithm to map Coarse-grained and all-atoms structures,[1] or Molecular Dynamics results showing the power of combining experimental and computational methods in the field of lipid membranes and peptide nanopores.[2-3]

Furthermore, several tools developed by the MD.USE Innovative Solutions, based on state-of-the art technologies such as Molecular Dynamics (MD), Virtual Reality (VR) and Augmented Reality (AR) will be presented. It is possible now to travel along complex molecular systems looking at them from different perspectives, orientations and positions in a fully immersive way. The visualization of molecular structures, such as cyclodextrins, in 360o and VR allow users immersing into an amazing experience. The creation of images in AR is now possible, opening the door to a new era in the way of presenting scientific papers or posters.

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Keywords: Molecular Dynamics, Coarse Grained, AR, VR

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Poster 03

Less is more: Coarse-grained integrative modelling of large biomolecular assemblies with HADDOCK

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Predicting the 3D structure of protein interactions remains a challenge in the field of computational structural biology. This is in part due to difficulties in sampling the complex energy landscape of multiple interacting flexible polypeptide chains. Coarse-graining approaches, which reduce the number of degrees of freedom of the system, help address this limitation by smoothing the energy landscape, allowing an easier identification of the global energy minimum. They also accelerate the calculations, allowing to model larger assemblies. Here, we present the implementation of the MARTINI coarse-grained force field for proteins into HADDOCK, our integrative modelling platform. Docking and refinement are performed at the coarse-grained level and the resulting models are then converted back to atomistic resolution through a distance restraint-guided morphing procedure. Our protocol, tested on the largest complexes of the protein docking benchmark 5, shows an overall _~7-fold speed increase compared to standard all-atom calculations, while maintaining a similar accuracy and yielding substantially more near-native solutions. To showcase the potential of our method, we performed simultaneous 7 body docking to model the KaiC-KaiB complex, integrating mutagenesis and hydrogen/deuterium exchange data from mass spectrometry with symmetry restraints, and validated the resulting models against a recently published cryo-EM structure.

Keywords: protein, protein interactions, HADDOCK, coarse, grain, docking

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Poster 04

Modeling structural and mechanical properties of recurent RNA motifs

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Recurrent RNA internal loops, such as C-loops [1] and kink-turns [2], are highly conserved key structural and functional elements in the ribosome, which are also being used as building blocks in artificial nanostructures. While their geometry has been partially characterized, their mechanical properties remain to be investigated.

We propose a method to evaluate global structure and elasticity of the internal loops [1]. A-RNA helices flanking the motif are modeled as rigid bodies. Their relative rotation and displacement dictated by the motif are described by a set of six interhelical coordinates. The deformation energy is assumed to be a general quadratic function of the given interhelical coordinates. The model parameters are inferred from atomistic molecular dynamics simulations of isolated motifs. C-loops show high twist as reported earlier, but also introduce modest bending and lateral displacement of the flanking helices. Bending and displacement are nearly isotropic and the overall stiffness is similar to control A-RNA helix. Kink-turns, on the other hand, exhibit sharp bend and displacement shows relatively high anisotropy. In general, Kink-turns are almost two times more flexible than C-loops and A-RNA helices. Our results can help to better understand the function of C-loops and kink-turns in the ribosome and can enable one to choose optimally stiff loop for use in nanostructures [1]. The approach can be extended to more complex structural motifs.

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Structural Refinement of Small Ribosomal Subunit Using Self-Guided Langevin Dynamics

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A central process in all living beings is protein synthesis which involves the ribosome machinery, transfer RNA, messenger RNA and various protein factors. [1] The main difficulty in understanding the translation of proteins is a lack of structural and dynamical information. However, with the advances in X-ray crystallography and cryo-EM microscopy, it is possible to obtain some insights and static snapshots of the translation process. Our work is focused on translation initiation, which is a rate-limiting step. The experimental Mechulam/Schmitt group in our department have derived a detailed structural model of the small ribosomal subunit (the 30S) of *Pyrococcus abyssi*. We are using molecular dynamics (MD) to study its structure, flexibility and function. The low-resolution experimental structure is being refined using a Molecular Dynamics Flexible Fitting method [2] implemented in Charmm, with the Self-Guided Langevin Dynamics method for enhanced sampling [3]. During the MD, the structure is constrained to stay within the cryo-EM electron density map. Since ribosomal complexes are extremely large, the solvent is described implicitly. We will describe results from our first simulations.

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Keywords: ribosome, structural refinement, MDFF, SGLD, molecular dynamics, implicit solvent

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Poster 06

Temperature Dependence of DNA Structure

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It is well known that the three-dimensional structure of DNA varies with temperature. In a recent work, our group studied the temperature dependence of DNA twist and demonstrated strong quantitative agreement between magnetic tweezer experiments and molecular dynamics simulations. However, precise quantification of the temperature-dependent global conformational characteristics that occur remains incomplete. Thus, in this work, we investigate the relationships between the global shape of the DNA double helix and both other local coordinate changes and backbone torsion angle substates. As the data source, we used atomic-resolution molecular dynamics simulations with the explicit inclusion of water and ions in the range of 7–47 ∘C. 3DNA software was used to extract time series of DNA local coordinates from the simulated data. MATLAB analysis showed that all global conformational characteristics changed almost linearly with temperature. Decomposition of the overall thermal changes to contributions from the local base pairs revealed that the global shape of DNA was dependent on changes in the structure of the individual substates rather than on changes in the population of the backbone substates.

Keywords: conformational characteristics of DNA, molecular dynamics simulations, temperature dependence

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