BP 9: Computational biophysics

Time: Tuesday 9:30–13:00 Location: H11

Invited Talk BP 9.1 Tue 9:30 H11

Biomolecular structure determination from single molecule X-ray scattering with three photons per image — •Helmut Grubmueller and Benjamin von Ardenne — Department of Theoretical and Computational Biophysics, Max Planck Institute for Biophysical Chemistry, Am Fassberg 11, 37077 Göttingen, Germany

Scattering experiments with femtosecond high-intensity free-electron laser pulses provide a new route to time resolved macromolecular structure determination. While currently limited to nano-crystals or virus particles, the ultimate goal is scattering on single biomolecules. The main challenge in these experiments is the extremely low signal-to-noise ratio due to the very low expected photon count per scattering image, often well below 100. We describe a correlation-based approach and show that three coherently scattered photons per image suffice for structure determination. Using synthetic scattering data of a small protein, we demonstrate near-atomic resolution of 3.3 A using 3.3×10^{10} coherently scattered photons from 3.3×10^9 images, which is within experimental reach. Our correlation approach is robust to additional noise from incoherent scattering.

BP 9.2 Tue 10:00 H11

Thermodynamics and conformations of homopolymeric polypeptides — •Arne Böker, Paul Käthner, and Wolfgang Paul — Martin-Luther-Universität Halle-Wittenberg

Although the number of structures in the PDB is continuously growing, the topic of protein folding still requires great attention and is being treated with a variety of methods. Especially the reasons for proteins to aggregate as amyloids are far from being understood. While aggregation is a collective feature of multiple molecules, the starting point must be a single chain, so understanding single molecule structure is a prerequisite for understanding aggregation. The stability of motifs such as β-sheets may give us insight into the formation and stability of aggregates.

For these reasons, we simulate different polypeptides (polyalanines/polyA, polyglutamines/polyQ and polyserines/polyS with 8 to 23 monomers) and investigate their thermodynamics and structure formation. We use a four-bead representation called PRIME20 (Cheon et al., 2010) together with a flat histogram Monte Carlo method (Liang et al., 2007) which provides full thermodynamic information over a broad temperature range.

We find that polyS and polyQ, disordered under physiological conditions, can fold into distinct ground states where polyS forms a helix similar to polyA while polyQ prefers a hairpin. β-type intermediates occur during folding of all our peptides. We also investigate the influence of end-attached spectroscopy dyes and solubility-enhancing residues and find significant deviations in the folded structures.

BP 9.3 Tue 10:15 H11

A framework for spatially embedded biological network growth — •Torsten Paul[1], Felix Repp[2], and Philip Kollmannsberger[1] — [1]Center for Computational and Theoretical Biology, University of Würzburg, Germany — [2]Department of Neurophysiology, University of Würzburg, Germany

Spatial biological networks are important for signaling, transportation and stability, and are found on many scales, from osteocytes and neuronal connections up to vasculature or roots. By combining image analysis of such multicellular networks with graph theory, they can be compared quantitatively to different random or regular networks. The biological interpretation of the results so far was limited, as we lack an appropriate model linking local cell behavior and tissue organization during growth to the resulting global network architecture. Here, we introduce a new 3D parallel simulation framework that aims to fill this gap. We model spatial network growth as a biased correlated random walk where growth direction and branching probability depend on the local environment, e.g. soluble cues, tissue anisotropy, or other cells. This is implemented by representing the environment as a multi-layer image from which gradients, structure tensors and other influencing parameters are calculated. Our generally applicable framework will help to better understand how biological network patterns depend on the growth rules under different environmental conditions, and to identify the biological cause of deviations from healthy network function.

BP 9.4 Tue 10:30 H11

Coarse-Grained Molecular Dynamics reveals the optimal folding pathways of self-entangled proteins — •Claudio Perego[1] and Raffaello Potestio[2] — [1]Polymer Theory Department, Max Planck Institute for Polymer Research, Mainz, Germany — [2]Physics Department, University of Trento, Trento, Italy

Among the known protein motifs, several structures exhibit a self-entangled backbone topology. Understanding how polypeptides can efficiently and reproducibly attain such topologies is a crucial biophysical challenge, which might shed new light on our general knowledge about protein folding. In this work we present a molecular dynamics method for finding the possible folding pathways of self-entangled proteins. The technique is based on a Coarse-Grained, minimalistic representation of the polypeptide chain, driven by a structure-based angular potential. The relative magnitude of these interaction potentials is optimized by means of an evolutionary strategy, aimed at maximizing the folding probability within the first stages of the dynamics. By means of this approach we construct a simple protein model that is capable of attaining the self-entangled structure in a reproducible and efficient way. At the same time the optimization process mimics the action of evolutionary pressure, that might have selected a specific folding pathway among all the possible routes. Applying this methodology to relevant test cases we retrieve indications on the optimal pathways chosen by self-entangled proteins to attain their native topology, and useful guidelines for simulations employing more detailed molecular models.

BP 9.5 Tue 10:45 H11

QM/MM free energy maps and nonadiabatic simulations for a photochemical reaction in DNA: cyclobutane thymine dimer — •Jesus I. Mendieta Moreno[1,2], Daniel G. Trabada[2], Jesus Mendieta[3], Paulino Gomez-Puertas[3], and Jose Ortega[2] — [1]FZU of the CAS, Prague, Czequia — [2]UAM, Madrid, Spain — [3]CBMSO, Madrid, Spain

The absorption of ultraviolet radiation by DNA may result in harmful genetic lesions that affect DNA replication and transcription, ultimately causing mutations, cancer, and/or cell death. We analyze the most abundant photochemical reaction in DNA, the cyclobutane thymine dimer, using hybrid quantum mechanics/molecular mechanics (QM/MM) techniques and QM/MM nonadiabatic molecular dynamics. We find that, due to its double helix structure, DNA presents a free energy barrier between nonreactive and reactive conformations leading to the photolesion. Moreover, our nonadiabatic simulations show that most of the photoexcited reactive conformations return to standard B-DNA conformations after an ultrafast nonradiative decay to the ground state. This work highlights the importance of dynamical effects (free energy, excited-state dynamics) for the study of photochemical reactions in biological systems.

Jesús I. Mendieta-Moreno et al, Quantum Mechanics/Molecular Mechanics Free Energy Maps and Nonadiabatic Simulations for a Photochemical Reaction in DNA: Cyclobutane Thymine Dimer. J. Phys. Chem. Lett. 2016 7, 4391-4397.

15 minutes break.

BP 9.6 Tue 11:15 H11

Fine- grained simulation of the microenvironment of vascularized tumors — •Thierry Fredrich[1], Edoardo Milotti[2], Roberto Chignola[3], and Heiko Rieger[1] — [1]Center for Biophysics & Theoretical Physics, Saarland University, D-66123 Saarbrücken — [2]Physics Department, Triest University, I-34127 Triest — [3]Department of Biotechnology, I-37134 Verona

The road to the understanding of cancer is long and we are just at the beginning, however the life science community provides more and more insight into the underlying processes causing the, not always, deadly modifications of organs, tissue, vasculature, cells, etc. We combined a lattice-free simulation of tumor cells (*VBL*) with a lattice based blood vessel dynamic simulation (*tumorcode*) to mimic vascularized solid tumors at tissue scale. We reproduced in vivo measurements of pH and partial oxygen pressure (P_{O2}) obtained by Jain et. al. and observe the formation of different ecological niches at very early stages of tumor growth which could be a source of tumor heterogeneity.

I will present the two models and their combination, and discuss first results.

BP 9.7 Tue 11:30 H11

The physics of brain folding — •Lucas da Costa Campos[1,2], Svenja Caspers[2,3,4], and Jens Elgeti[2] — [1]Institute of Neuroscience and Medicine (INM-1), Forschungszentrum Jülich, Jülich, Germany — [2]Institute for Complex Systems (ICS-2), Forschungszentrum Jülich, Jülich, Germany — [3]Institute for Anatomy I, Medical Faculty, Heinrich-Heine University Düsseldorf, Germany — [4]JARA-BRAIN, Jülich-Aachen Research Alliance, Jülich, Germany

Humans possess the most folded brain among the primates. In humans, misfolding of the brain is strongly correlated with several maladies. Folding itself, however, is a physical process. One proposed mechanism is that of differential growth. Like a bimetallic strip, the outer gray matter expands more during development than the inner white matter. This leads to residual stress, and consequentially, to buckling.

We explore this hypothesis using an incompressible Neo-Hookean finite element model. Our system consists of two layers with distinct thicknesses, representing gray matter and white matter, where only the gray matter grows.

Brain folding is further complicated by spatial inhomogeneities in the cortex and its growth. We model these by sinusoidal profiles of cortical thickness or growth rate. In both cases, competition between distinct length scales proves crucial for the formation of sulci-like structures. We quantify the resulting patterns by measuring the curvature and thickness along the layers interface in the buckled system and analyze their correlations.

BP 9.8 Tue 11:45 H11

Numerical simulations to extract cell viscosity from microfluidic experiments — •Lucas D. Wittwer[1,2], Sebastian Aland[2], and Jochen Guck[1] — [1]BIOTEC, Center for Molecular and Cellular Bioengineering, TU Dresden, Germany — [2]Faculty of Informatics / Mathematics, University of Applied Science Dresden, Germany

The mechanical properties of biological cells are promising biomarkers to differentiate for example cell phenotypes, cell states or between healthy and unhealthy cells with applications ranging from research facilities to medical laboratories. Real-time deformability cytometry (RT-DC) allows probing the mechanical characteristics of ~1000 cells/s by imaging the cells when flowing through a microfluidic channel. The observed deformation can be used to infer the mechanical properties. So far, the expected deformation has been analysed theoretically and numerically assuming the cell to be a homogeneous elastic material. Here, we extend the mathematical framework to include the viscosity of the cell based on a fluid-structure interaction (FSI) simulation. In this talk, we present the extended numerical model, compare it with experimental results and illustrate the new possibilities to infer viscosity from real-time measurements in RT-DC.

BP 9.9 Tue 12:00 H11

A polarizable MARTINI model for monovalent ions in aqueous solution — Julian Michalowsky[1], Johannes Zeman[1], Christian Holm[1], and •Jens Smiatek[1,2] — [1]Institute for Computational Physics, University of Stuttgart, Germany — [2]Helmholtz-Institute Münster: Ionics in Energy Storage (HIMS - IEK 12), Forschungszentrum Jülich, Germany

We present a new polarizable coarse-grained MARTINI force field for monovalent ions, called refIon, which is developed mainly for the accurate reproduction of electrostatic properties in aqueous electrolyte solutions. The ion model relies on full long-range Coulomb interactions and introduces satellite charges around the central interaction site in order to model molecular polarization effects. All force field parameters are matched to reproduce the mass density and the static dielectric permittivity of aqueous NaCl solutions up to moderate salt concentrations.. Our model is validated with regard to analytic solutions for the ion distribution around highly charged rod-like polyelectrolytes in combination with atomistic simulations and experimental results concerning structural properties of lipid bilayers in presence of distinct salt concentrations. Further results regarding the coordination numbers of counterions around distinct polyelectrolytes also highlight the applicability of our approach. The introduction of our force field allows us to eliminate heuristic scaling factors, as reported for previous MARTINI ion models in terms of effective salt concentrations, and in consequence provides a better agreement between simulation and experimental results.

BP 9.10 Tue 12:15 H11

Decompostion of the proton transfer dynamics in the Zundel cation — •Florian N. Brünig and Roland R. Netz — Institut für Theoretische Physik, Freie Universität Berlin

Although extensively studied in experiment and theory, the dynamics of excess protons in water and in particular the proton transfer between molecules remain elusive. The direct intermediate of the proton transfer in water is indisputably the $H_2O_5^+$ or Zundel cation, which has recently been studied experimentally by infrared spectroscopy. The experiments have been interpreted in terms of a low-barrier double-well potential for the excess proton caused by the two adjacent water molecules. We investigate the proton transfer mode by ab-initio simulations of a single Zundel cation and decomposition techniques. We compare calculated spectra with analytic theory that predicts a low frequency spectral tail due to barrier-crossing events. The fast exchange dynamics produces a high-frequency spectral contribution that can be interpreted using a one-dimensional generalized Langevin equation.

BP 9.11 Tue 12:30 H11

Optimized all-atom force fields for Mg^{2+} based on water exchange properties — •Kara K. Grotz and Nadine Schwierz — Department of Theoretical Biophysics, Max Planck Insitute of Biophysics, Frankfurt am Main, Germany

Magnesium cations are essential in many vital processes. Binding of a Mg^{2+} ion to the functional group on a biomolecule involves the removal of one water molecule from the first hydration shell. With the current force fields, this initial step takes about a microsecond. Hence, the description of binding events in a statistically meaningful way or the exploration of different binding sites of complex nucleic acids is beyond reach of Molecular Dynamics simulations. Here, we develop two improved Mg^{2+} force fields in combination with TIP3P water as required for many biomolecular simulations. For both models, we reproduce the experimental solvation free energy, the number of water molecules in the first hydration shell, their mean distance to the $^{2+}$ cation, and the diffusion coefficient. Modifying the Lorentz-Berthelot combination rules and using Kirkwood-Buff theory allows us to simultaneously reproduce the experimental activity derivatives. In addition, our first parameter set captures experimentally determined water exchange rates while the second parameter set enables us to accelerate the rate. Thereby, the second parameter set allows us to speed up simulations of binding events without changing thermodynamic properties.

BP 9.12 Tue 12:45 H11

Influence of DNA rotation and solvent on the electronic transport properties of diamondoid-functionalized electrodes — •Frank C. Maier, Maofeng Dou, and Maria Fyta — Institute for Computational Physics, Stuttgart, Germany

Diamondoid-functionalized gold electrodes have the potential to identify single DNA nucleotides by measuring the electronic tunneling current across the electrodes. The diamondoid functionalization can prolong the measurement time and enhance the nucleotide specificity in the current signals by forming hydrogen bonds with single nucleotides. In this study, we assess the influence of a solvent environment and the dynamics of a DNA molecule within the electrodes on their transport properties. For this, we assume a water solvent within the electrodes and evaluate the chance in the conductance. In order to account for the DNA dynamics, we allow the single DNA nucleotides to rotate within the electrode gap and monitor the changes in the corresponding transport properties. Our results are based on quantum-mechanical simulations implementing the density functional theory, together with the non-equilibrium Green's function scheme, as well as Quantum-Mechanics/Molecular mechanics simulations. In the end we discuss the relevance of our results in view of DNA sequencing with nanopores, in which our diamondoid-functionalized electrodes are embedded.