BP 12: Computational Biophysics I

Time: Tuesday 9:30–13:00 Location: H 1058

BP 12.1 Tue 9:30 H 1058

Langevin modeling of targeted molecular dynamics: a novel approach to calculate equilibrium free energies from non-equilibrium simulations — •Steffen Wolf and Gerhard Stock — Bimolecular Dynamics, Institute of Physics, Albert-Ludwigs-University Freiburg, Germany

We present an approach to calculate free energy surfaces based on non-equilibrium biased molecular dynamics simulations. Based on a comparison of Jarzynskis equality and the Langevin equation we derive an expression for non-equilibrium friction factors $\Gamma_{\mathrm{NEQ}}(x)$. Force fluctuations $\delta f(t)$ of a simulated trajectory ensemble were derived from targeted molecular dynamics simulations as constraint forces using a holonomic constraint $\Phi(t) = (x(t) - x_0(t) - v_c t)^2 = 0$ with a constant constraint velocity v_c. Using a NaCl/water test system, we show that a surprisingly high accuracy in the prediction of the equilibrium free energy profile can be achieved with a relatively small number of $N = 30$ simulations at comparatively high constraint velocities of $>$10 nm/ns. Non-equilibrium friction profiles however need at least $N = 500$ simulations to converge. Comparison with equilibrium simulations shows a general agreement between non-equilibrium and equilibrium-derived friction factors for $v_c \to 0$. The non-equilibrium factors however contain intrinsic constraint velocity dependence, and outperform equilibrium factor-based corrections. Our approach allows for the calculation of near-continuous $\Gamma_{\mathrm{NEQ}}(x)$ profiles directly from non-equilibrium trajectories, and thus for the on-the-fly correction of non-equilibrium simulations to obtain equilibrium free energy profiles.

BP 12.2 Tue 9:45 H 1058

Refolding dynamics of molecular constructs after a force quench — •Ken Schäfer and Gregor Diezemann — Institut fuer Physikalische Chemie, Johannes Gutenberg-Universität Mainz, Duesbergweg 10-14, D-55128 Mainz, Germany

In typical force-probe molecular dynamics simulations (FP-MD) one end of a molecular complex is fixed in space and another end is pulled away with a constant velocity. This allows to gather detailed atomistic information about the mechanical unfolding of the complex and the corresponding free energy landscape.

The folding process can be studied by first mechanically unfolding the system and afterwards releasing the external force either completely or to a finite value. This method allows to study the mechanical folding pathway in a systematic way as a function of the quench force. In FP-MD simulations this is of particular interest because it allows to consider forces much smaller than typically used in the standard protocol with a time-dependent force.[1]

We apply the method to study the refolding transition in a calixarene catenane system investigated earlier[2] and extract the kinetic rates for the transition that are analyzed using stochastic models.

[1] C. Hyeon, G. Morrison, D. Thirumalai, PNAS, 2009, 106, 48.
[2] T. Schlesier et al., 2011 J. Phys. Chem. B, 115, 6445.

BP 12.3 Tue 10:00 H 1058

G-PCCA - a generalized Markov state modeling approach for both equilibrium and non-equilibrium systems — •Bernhard Reuter[1], Konstantin Fackeldey[2,3], Susanna Röblitz[2], Marcus Weber[2], and Martin E. Garcia[1] — [1]Theoretical Physics II, University of Kassel, Germany — [2]Zuse Institute Berlin (ZIB), Germany — [3]Institute of Mathematics, Technical University Berlin, Germany

Markov state models (MSMs) have received an ongoing increase in popularity in recent years as they enable the conflation of data from simulations of different length and the identification and analysis of the relevant metastabilities and kinetics of molecular systems. However, so far methods and tools for building MSMs, like PyEMMA and MSMBuilder, are restricted to equilibrium systems fulfilling the detailed balance condition. This constitutes a severe constraint, since molecular systems out of equilibrium, e.g. disturbed by an external force, have attracted increasing interest. To overcome this limitation we have developed and implemented - in Python and MATLAB - a generalization of the widely used robust Perron cluster cluster analysis (PCCA+) method, termed generalized PCCA (G-PCCA). This method, based on the utilization of Schur vectors instead of eigenvectors, can handle both data from equilibrium and non-equilibrium simulations. G-PCCA is able to identify dominant structures in a more general sense, not limited to the detection of metastable states, unraveling cyclic processes. This is exemplified by application of G-PCCA on non-equilibrium molecular dynamics (NEMD) data of the Amyloid-beta peptide, periodically driven by an oscillating electric field.

BP 12.4 Tue 10:15 H 1058

Structural-kinetic relationships determine consistent interpretations of coarse-grained peptide kinetics — •Joseph Rudzinski and Tristan Bereau — Max Planck Institute for Polymer Research, Ackermannweg 10, 55128 Mainz

Coarse-grained molecular simulation models have provided tremendous insight into the complex behavior of protein systems, but lack a straightforward connection to the true dynamical properties of the system. This lack of consistent dynamics severely limits coarse-grained models from providing accurate interpretations for kinetic experiments. In this work, we perform a detailed investigation into the kinetic properties of secondary structure formation generated by molecular simulation models. Our strategy is to systematically vary force-field parameters of a simple, native-biased coarse-grained model to identify relationships between the emergent structural, kinetic, and thermodynamics properties. We utilize Markov state models to efficiently and systematically assess the system's kinetic properties. Our investigation reveals robust structural-kinetic relationships that can be exploited to guarantee consistent kinetics through the reproduction of particular structural properties. These remarkable relationships are determined by the physics of the model, which shapes the free-energy landscape and restricts the attainable kinetic properties. Our results suggest an approach for constructing kinetically-accurate models that extends the capabilities and scope of current coarse-grained peptide models.

Invited Talk BP 12.5 Tue 10:30 H 1058

Atomistic Simulation of Biomolecular Function: Ribosomal translation, Intrinsically Disordered Proteins, and a Dynasome Perspective — •Helmut Grubmüller — 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 and the action of antibiotics work at the molecular level. We show that tRNA translocation between A, P, and E sites is rate limiting, and identified dominant interactions. We also show that the so-called L1 stalk actively drives tRNA translocation, and that 'polygamic' interactions dominate the intersubunit interface, thus explaining the detailed interaction free energy balance required to maintain both controlled affinity and fast translation We will further suggest a new combined mechanism for translational stalling due to erythromycin bound in the exit tunnel. 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.

15 min. break

BP 12.6 Tue 11:15 H 1058

Specific RNA-cation interactions: Individual binding site affinities from molecular dynamics simulation — •Sergio Cruz-León and Nadine Schwierz — Department of Theoretical Biophysics, Max Planck Institute for Biophysics, Max-von-Laue-Str. 3, 60438 Frankfurt, Germany

Metal cation-RNA interactions are essential for RNA folding and function. In this research, cation-mediated specific interactions between common RNA structural motifs and a set of biologically relevant metal cations including Li^+, Na^+, K^+, Cs^+, Mg^{2+}, Ca^{2+}, Sr^{2+} and Ba^{2+} are studied with all atom molecular dynamics simulations. Combining advanced sampling techniques and recent force fields for metal cations developed in our group, we investigate ion binding to individual binding sites on RNA by calculating ion binding affinities and kinetic rate coefficients. The calculated binding affinities agree well with available experimental data. Specifically bound cations and ions that diffusively surround the RNA affect the end-to-end distance of double stranded

RNA and RNA-RNA interactions consistently with reported experimental findings. This detailed understanding of the metal cation-RNA interactions and its driving forces may provide a starting point to explore the exciting possibility to control structure formation and biological functions which have applications in nanotechnology and RNA based tools medicine.

BP 12.7 Tue 11:30 H 1058

On the nature of cytosine pairing in DNA structures — Miriam Kohagen and •Jens Smiatek — Institute for Computational Physics, University of Stuttgart, D-70569 Stuttgart, Germany

Besides protonated cytosine pairs, recent experimental results indicate that non-Watson-Crick DNA structures can also be stabilized by intercalated metal cations. Whereas Au+, Cu+ and Ag+ can be regarded as stabilizing agents, alkali metal ions like Na+, Li+ and K+ are known as destabilizers. In this article, we rationalize the experimentally observed behavior with the help of density functional theory calculations. Our results demonstrate the dominance of covalent electrostatic bonds, meaning that a significant amount of electron density has to be located on the cations in order to stabilize cytosine pairs. Further findings imply that mixed higher electron orbitals, in addition to a pronounced electronegativity of the cations, are of fundamental importance for the binding mechanism. The outcomes of our calculations establish a consistent theoretical framework to understand the experimentally observed behavior, which is also important to achieve a more detailed understanding of nucleobase pairing in general.

BP 12.8 Tue 11:45 H 1058

Loop formation of polyglutamines in the PRIME20 model — •Arne Böker and Wolfgang Paul — Martin-Luther-Universität Halle-Wittenberg, 06099 Halle

Much effort has recently been put into understanding amyloid formation in polypeptides. The amyloid state is an aggregated structure of polypeptides and usually differs from the native state. Amyloid formation can have various effects, beneficial as well as damaging, including diseases such as Huntington's chorea, which is associated with an aggregated state of extended polyglutamine (polyQ) sequences. Loop structures or even β turns of single polyQ molecules may act as templates for aggregation, which motivates experimental investigation by energy transfer methods as well as our simulations.

We perform thermodynamic simulations of single polyQ chains represented by the intermediate-resolution PRIME20 model[1] using the SAMC[2] variation of Wang-Landau Monte Carlo sampling which provides insight into different statistical ensembles at the expense of dynamic information. Our results for the end-to-end distance distribution at physiological conditions agrees reasonably well with experimental findings. In this temperature range, the single-chain morphology for the chain lengths we studied is not yet dominated by hairpin structures which are formed at lower temperatures.

[1]M. Cheon, I. Chang, C. K. Hall, PROTEINS **78**(2010):2950

[2]B. Werlich, T. Shakirov, M. P. Taylor, W. Paul, Comp. Phys. Comm. **186**(2015):65

BP 12.9 Tue 12:00 H 1058

Pro32 isomerisation effects on β2-microglobulin: a Metadynamics investigation — •Maria Celeste Maschio[1], Federico Comitani[2], Carla Molteni[3], and Stefano Corni[4] — [1]Dept. FIM, University of Modena and Reggio Emilia, Italy — [2]Dept. Chemistry, University College London, UK — [3]Dept. Physics, King's College London, UK — [4]Dept. Chemistry, University of Padova, Italy

β2-microglobulin (β2-m) is the protein responsible for the Dialysis Related Amyloidosis disease. The isomerisation of a specific proline, Pro32, is a debated amyloidosis triggering factor, inducing the β2-m aggregation. In this work, we investigated the structural rearrangements observed in the protein upon isomerisation of Pro32. Metadynamics simulations of the β2-m wild type (WT), the D76N amyloidogenical mutant and the W60G aggregation-resistant mutant were run to shed light on the structural and dynamical changes upon isomerisation and to identify the effects of mutations on the relative free energies of the cis and the trans isomers.

[1] Stoppini M et al, J Biol Chem, 290(16), 2015 [2] Melis C et al, J Phys Chem B, 113(35), 2009 [3] Laio A et al, PNAS, 20(99), 2002

BP 12.10 Tue 12:15 H 1058

Metadynamics Simulations of the Fibrinogen Protomer — •Timo Schäfer[1,2], Lorenz Ripka[1], Friederike Schmid[1], and Giovanni Settanni[1,3] — [1]Johannes Gutenberg-University Mainz — [2]Graduate School Materials Science in Mainz — [3]Max Planck Graduate Center with the Johannes Gutenberg-University Mainz

Fibrinogen is a dimeric multi-chain serum protein that polymerizes into fibrin when activated by thrombin as part of the coagulation cascade. Fibrinolysis, the cleavage of fibrin by the enzyme plasmin, controls the dissolution of blood clots. While the major factors contributing to fibrin formation and dissolution have been identified, the atomistic details of these mechanisms are largely unknown.

Here, the connection between structure and function of fibrinogen is studied using classical atomistic molecular dynamics simulations coupled to metadynamics, a technique that allows for a thorough exploration of the important degrees of freedom of the system. Based on our previous characterization of a hinge along the coiled-coil region of the fibrinogen protomer, we used metadynamics to explore the major degrees of freedom related to this hinge, represented by the two largest principal components of motion. The simulations reveal the presence of two specifically distinct modes of bending, characterized by a different loss of secondary structure and exposure of plasmin cleavage sites. The bending modes occur in plane to the available models of double-stranded fibrin protofibrils. We show how they could be integrated into available models of fibrin protofibril formation and play a role in fibrinolysis

BP 12.11 Tue 12:30 H 1058

Integration of SAXS Data into Biomolecular Simulations — •Marie Weiel, Ines Reinartz, and Alexander Schug — Karlsruhe Institute of Technology, Karlsruhe, Germany

Structural analyses in biophysics aim at revealing the interrelation between a macromolecule's dynamic structure and its biological function. Small-angle X-ray scattering (SAXS) is a useful experimental approach to this and complementary to common high-resolution techniques such as X-ray crystallography and NMR spectroscopy. In order to effectively interpret scattering intensities in terms of structural models, we include the limited information from SAXS into molecular dynamics (MD) simulations using computationally efficient native structure-based models (SBMs). A particular initial structure is defined as the global minimum in a smooth single-basin energy funnel dominated by native interactions. To incorporate information from SAXS, a bias term is added to the potential so as to energetically favour conformations reproducing the original target intensity. Dynamically fitting an initial structure to the scattering curve within MD, we obtain physical atomistic conformations according to the experimental input data. In this vein, SAXS data may be reasonably interpreted whilst simultaneously retaining chemical knowledge and sampling power of molecular force fields. Giving fast and reliable structure predictions for transiently populated conformations, we hope to make a significant contribution to unraveling the relation between macromolecular structure and function.

BP 12.12 Tue 12:45 H 1058

Terminal Electron-Proton Transfer Dynamics coupled to Quinone reduction in Respiratory Complex I — •Ana Patricia Gamiz-Hernandez[1], Alexander Jussupow[1], Mikael P. Johansson[2], and Ville R. I. Kaila[1] — [1]Department of Chemistry, Technical University of Munich, Lichtenbergstr. 4, D-85747, Garching, Germany — [2]Department of Chemistry, University of Helsinki, P. O. Box 55, FI-00014 Helsinki, Finland

Complex I (NADH:ubiquinone oxidoreductase) contains 8-9 iron sulfur clusters (ISC) in its hydrophilic domain responsible of transferring two electrons from NADH/FMN couple to the quinone binding site, thus initiating the signal that triggers proton pump across its membrane. Although the exact coupling for this long-range proton-electron transfer process remains unclear, emerging data indicates that the initial quinone (Q) reduction to quinol (QH2) process plays a central role in activating the proton pumping machinery. In order to probe the energetics, dynamics, and molecular mechanism for the proton-coupled electron transfer (PCET) process linked to Q reduction, we employ here multi-scale quantum and classical molecular simulations, to model the relevant electronic states from Q to QH2 that may play a role in the activation of proton pump. We find that conformational changes in the hydrogen-bonded Q-binding modes regulate the rate of eT from the terminal N2 iron-sulfur center. Our combined data reveal how the dynamics of complex I-bound Q modulates the rate of terminal electron transfer, and how conserved residues in the Q-chamber contribute to the overall PCET process.