BP 25: Protein Structure and Folding

Time: Thursday 14:30–17:00 Location: PC 203

BP 25.1 Thu 14:30 PC 203

Transition states in protein folding — •Thomas Weikl — Max-Planck-Institut für Kolloid- und Grenzflächenforschung, Abteilung Theorie und Bio-Systeme, Wissenschaftspark Golm, 14424 Potsdam

Conformational transitions of proteins are often apparent two-state processes. Examples are the folding and unfolding of small single-domain proteins, or the opening and closing of ion channels. The dynamics of two-state processes is thought to be governed by a transition-state barrier between the two states. Transition states are short-lived and cannot be observed directly in experiments. However, a mutational analysis of the two-state dynamics can provide indirect access. In a mutational analysis, experimentalists measure the effect of point mutations on the folding and unfolding rates of small proteins, or the opening and closing rates of ion channels. I will present models that help to reconstruct folding transition states from mutational data. The models are based on identifying cooperative substructural elements of proteins, and on calculating mutation-induced free-energy changes for these elements.

References:

[1] C. Merlo, K. A. Dill, and T. R. Weikl, PNAS 102, 10171 (2005).
[2] T. R. Weikl and K. A. Dill, J. Mol. Biol. 365, 1578 (2007).
[3] T. R. Weikl, Biophys. J., in press (2008).

BP 25.2 Thu 14:45 PC 203

Algorithm for selection of fast folding proteins — •Dmitry Gridnev and Martin Garcia — Kassel University, Heinrich-Plett-Str. 40, Germany

We discuss the following problem: from a large number of given amino acid chains select potentially good folders. In the framework of the lattice model of proteins we propose an algorithm, which uses the Monte Carlo dynamics and tests the rate of convergence of an amino acid chain in the configuration space. To test this algorithm we have hidden one known good folder among one thousand of other chains with a random amino acid decomposition. Our results show that the designed good folding sequence comes on top in the list of folders from good to bad. We also discuss how this method could be generalized to more sophisticated atomistic models.

BP 25.3 Thu 15:00 PC 203

Relation of Evolutionary Dynamics to Molecular Mechanics — •Kay Hamacher — Bioinformatics & Theo. Biology Group, Dept. of Biology, Technische Universität Darmstadt, Schnittspahnstr. 10, 64287 Darmstadt, Germany

We investigate the connection between sequence evolution under selective pressure induced by drugs and the functional and molecular-stability characteristics of a protein.

To this end we analyze sequence data of the human immunodeficiency virus (HIV) type 1 protease for more than 45,000 patients. We then formulate a chemo-physical-model for the stability and the functional modes of the protease and correlate the findings on the sequence evolutionary dynamics to extensive *in-silico*-mutagensis studies performed with this chemo-physical-model. First we derive a physical explanation for the particular important mutation V82F-I84V.

In a second step we discuss interactions in the β-sheet dimerization interface to be most important for maintaining function and stability of the protease. These interactions are at the same time evolutionary conserved - implications of and comparisons to experimental and other theoretical results are finally discussed.

BP 25.4 Thu 15:15 PC 203

Thermodynamics and kinetics of a protein-like heteropolymer model with two-state folding characteristics — Anna Kallias, •Michael Bachmann, and Wolfhard Janke — Institut für Theoretische Physik, Universität Leipzig, Postfach 100 920, D-04009 Leipzig

We present results of Monte Carlo computer simulations of a coarse-grained hydrophobic-polar Gō-like heteropolymer model and discuss thermodynamic properties and kinetics of an exemplified heteropolymer, exhibiting two-state folding behavior [1]. We find that thermodynamic and kinetic properties as, for example, the folding temperature within this model, are quantitatively consistent. It turns out that general, characteristic folding features of realistic proteins with a single free-energy barrier can also be observed in this simplified model, where the folding transition is primarily driven by the hydrophobic force. As further recent results [2], our study shows that characteristic features of protein folding are intrinsic properties of heteropolymers and thus even observable on mesoscopic scales.

[1] A. Kallias, M. Bachmann, and W. Janke, J. Chem. Phys., in print (2007).
[2] S. Schnabel, M. Bachmann, and W. Janke, Phys. Rev. Lett. **98**, 048103 (2007).

BP 25.5 Thu 15:30 PC 203

Insights from atomistic computer simulations of halophilic proteins — •Joachim Dzubiella — Physics Department, Technical University Munich, Germany

Halophilic (salt-loving) proteins, typically found in Archaea, can maintain their native structure and function in aqueous environment only at relatively high salt concentrations (>1-2M). As they are highly negatively charged at physiological conditions the competition between hydrophobic and hydrophilic solvation is strongly amplified and tuned by salt type and concentration. By performing atomistic molecular dynamics (MD) computer simulations the influence of salt on effective interactions between amino acids, protein secondary structures, and the stability of small coiled-coil proteins is investigated. Possible salt-induced specific and non-specific (de)stabilization mechanisms are identified and critically discussed.

BP 25.6 Thu 15:45 PC 203

Molecular machines involving electron tunneling — •Igor Goychuk — Institut für Physik, Universität Augsburg, Germany

ATP-driven molecular machinery of living cells involves various molecular motors operating far from the thermodynamic equilibrium. They are generally believed to be essentially classical nanoengines. Nitrogenase molecular machines present, however, a clear counter-example because of the long-range electron tunneling involved in the overall reaction of nitrogen fixation (ammonia production) which these enzymes perform: the energy derived from ATP hydrolysis is used to pump electrons into the nitrogenase reaction center. The theory of quantum dissipative dynamics driven by non-equilibrium fluctuations [1] presents a general theoretical framework for such and similar electron tunneling pumps. I will discuss a tentative mechanism [2,3] based on the stochastically driven spin-boson model [4] and general principles of the free energy transduction in biology [5].

[1] I. Goychuk, P. Hänggi, Adv. Phys. **54**, 525 (2005), and references therein.
[2] I. V. Kurnikov, A. K. Charnley, D. N. Beratan, J. Phys. Chem. B, **105**, 5359 (2001).
[3] I. Goychuk, Molecular Simulation **9**, 717 (2006).
[4] I.A. Goychuk, E.G. Petrov, V. May. J. Chem. Phys. **103**, 4937 (1995); *ibid.* **106**, 4522 (1997); Phys. Rev. E **52**, 2392 (1995), *ibid.* **56**, 1421 (1997).
[5]T.L. Hill, Free Energy Transduction in Biology (Academic Press, New York, 1977).

BP 25.7 Thu 16:00 PC 203

Protein structure prediction using structure profiles — •Katrin Wolff[1], Andrea Cavalli[2], Harri Hopeauroho[2], Michele Vendruscolo[2], and Markus Porto[1] — [1]Institut für Festkörperphysik, Technische Universität Darmstadt, Germany — [2]Department of Chemistry, University of Cambridge, UK

Protein structure predictors using knowledge-based energy functions and homology modelling have faced huge progress over the last few years whilst still allowing for further improvement. Here, we investigate the possibility to improve an existing predictor by incorporating information from structure profiles. A specific class of such profiles can be used to reconstruct the protein structure's contact matrix [1], from which the three-dimensional structure can be efficiently recovered [2]. Such profiles can be predicted to good accuracy from sequence (see e.g. [3]). It therefore seems promising to include profile information into existing predictors. Using the program collection 'almost' [4] we perform a series of prediction steps consisting of Monte Carlo-minimization with fragment insertion, filtering by the structure profile's cost function and subsequent refinement of predicted structures. We compare

conventionally predicted structures to those including the structure profile as an additional input for several known protein structures and show that RMSDs to the target structure significantly decrease.

[1] M. Porto *et al.*, Phys. Rev. Lett. **92**, 218101 (2004).
[2] M. Vendruscolo *et al.*, Fold. & Des. **2**, 295 (1997).
[3] A. R. Kinjo *et al.*, BMC Bioinformatics **7**, 401 (2006).
[4] A. Cavalli *et al.*, Proc. Nat. Acad. Sci. **104**, 9615 (2007)

BP 25.8 Thu 16:15 PC 203

Global Dynamics of Yeast Alcohol Dehydrogenase — •Biehl Ralf[1], Hoffmann Bernd[2], Fallus Peter[3], Monkenbusch Michael[1], Merkel Rudolf[2], and Richter Dieter[1] — [1]Institut für Festkörperforschung, Forschungszentrum Jülich, Germany — [2]Institut für Bio- und Nanosysteme, Forschungszentrum Jülich, Germany — [3]Institut Laue-Langevin, Grenoble, France

The dynamics of proteins is a keystone to the understanding of their function as nanomachines or while metabolizing toxic by-products. To understand these processes we need information on length scales comparable to the size of the protein, which determine their functionality. Neutron spin echo spectroscopy is a versatile tool to determine the dynamics of macromolecules on these nanometer length and a nanosecond timescale. We will present NSE results from the protein Yeast Alcohol Dehydrogenase, which is a compact tetramer build up from 2 dimeric subunits involved in the production of ethanol. It binds the cofactor NAD in a cleft before catalysing the ethanol production. At low concentration around 1% the protein dynamics is observable with only small influence of protein-protein interactions at lowest q. The main characteristics of the protein dynamics can be described as the translational diffusion at low q and additional rotational diffusion at higher q, compatible with a rigid body model. We find additional dynamics at the onset of rotational diffusion, which is modelled in a first approach by a contribution due to elastic normal modes. The influence of the bound cofactor leads to a shift of the elastic contribution to higher q attributed to stronger coupling between the main domains.

BP 25.9 Thu 16:30 PC 203

Accurate sequence alignment statistics for different protein models — •Stefan Wolfsheimer[1], Inke Herms[2], Sven Rahmann[3], and Alexander K Hartmann[1] — [1]Institut für Physik, Universität Oldenburg, Germany — [2]AG Genominformatik/COMET, Technische Fakultät,Universität Bielefeld, Germany — [3]Fachbereich Informatik, TU Dortmund, Germany

Searching for homologous sequences or identifying proteins are well studied fields in bioinformatics. For these purposes a large sequence database is searched with a query by sequence alignment algorithms. The Smith-Waterman algorithm is a famous representative of those. A meaningful interpretation of the score is given by a p-value, which states the probability of the score within a selected null model.

Exact results are only known for gapless alignment of infinitely long uncorrelated protein models, where the amino acids are independent and identically distributed (i.i.d.). For this case a Gumbel distribution is expected. It turned out that real proteins do not fulfill these restrictions: first they are finite and secondly the i.i.d. assumption might not be the best description. Therefore we study more complex systems which incorporate information from secondary structure annotation to obtain a more plausible null model.

By generalized ensemble Monte Carlo simulations we obtain the score distributions down to very small probabilities ($p \sim 10^{-100}$). We find strong deviations from the expected form in the rare-event tail. Our results indicate that p-values are overestimated in the high scoring regime, when assuming a Gumbel extrapolation.

BP 25.10 Thu 16:45 PC 203

MONTECARLO SIMULATIONS OF PROTEIN FOLDING UNDER CONFINEMENT — •Pedro Armando Ojeda May[1], Aurora Londono[2], Nan-Yow Chen[3], and Martin Garcia Rimsky[1] — [1]Kassel Universitaet, Heinrich-Plett-St- 40 34132 Kassel — [2]Department of Molecular Biology, IPICYT Mexico — [3]Academia Sinica, Taiwan

We present a theoretical investigation of the folding of small proteins assisted by chaperones. We describe the proteins in the framework of an effective potential model which contains the Ramachandran angles as degrees of freedom. The cage of chaperonins is modeled by an external confining potential which is also able to take into account hydrophobic and hydrophilic effects inside the cavity. Using the Wang-Landau algorithm [Phys. Rev. Lett. **86**, 2050 (2001)] we determine the density of states $g(E)$ and analyze in detail the thermodynamical properties of the confined proteins for different sizes of the cage. We show how the confinement through the chaperon dramatically reduces the phase space available for the protein leading to a much faster folding process. Slightly hydrophobic cages seem to make the native structure more stable. However, not any confining potential helps folding. If the inner walls of the cage are strongly hydrophobic, a denaturation process is induced, in which the proteins partially unfold and stick to the walls.