intermolecular attractions and repulsions that antibodies undergo in highly concentrated solutions.

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Melatonin Counteracts Cholesterol's Effects on Lipid Membrane Structure

Elizabeth Drolle[1], Norbert Kučerka[2,3], Youngjik Choi[1,4], John Katsaras[5], Zoya Leonenko[1,4].
[1]University of Waterloo, Waterloo, ON, Canada, [2]Canadian Neutron Beam Centre, Chalk River, ON, Canada, [3]Comenius University, Bratislava, Slovakia, [4]Waterloo Institute of Nanotechnology, Waterloo, ON, Canada, [5]Oak Ridge National Laboratory, Oak Ridge, TN, USA.

The cell membrane plays an important role in amyloid toxicity in relation to Alzheimer's disease. The membrane's composition and the inclusion of small molecules, such as melatonin and cholesterol, may alter the membrane's structure and physical properties, affecting its interaction with amyloid peptides. Both melatonin and cholesterol have been linked to amyloid toxicity. Melatonin has been shown to have a protective role against amyloid toxicity, while the underlying molecular mechanism of this protection is still not well understood. Here we have studied the non-specific interaction of melatonin and cholesterol with a model lipid membrane. We used small-angle neutron diffraction (SAND) from oriented lipid multilayers and small-angle neutron scattering (SANS) from unilamellar vesicles experiments to elucidate the structure of DOPC and DPPC model membrane in order to determine the effects of melatonin and cholesterol. From the present study we conclude that cholesterol and melatonin affect the lipid membrane differentially. Specifically, the incorporation of melatonin results in membrane thinning, in stark contrast to the increase in membrane thickness induced by cholesterol. This very different response of membrane thickness to cholesterol and melatonin may help to understand their relation to amyloid toxicity.

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Low Noise, High throughput Small-Angle Neutron Scattering of Protein in Solution

Shuo Qian, Sai Venkatesh Pingali, Volker Urban.
Oak Ridge National Laboratory, Oak Ridge, TN, USA.

Small-Angle Neutron Scattering (SANS) is well-suited to study structure and function of protein in solution by exploiting the natural scattering contrast difference between proteins and other biomolecules such as lipids and nucleic acids. The combination of high neutron flux and low experimental background makes the Bio-SANS instrument at ORNL's High Flux Isotope Reactor (HFIR) an ideal tool to study proteins and other biomolecules within complex biological assemblies and composites, in situ and in-vivo. The procedures used for protein solution scattering at the Bio-SANS are presented here. The scattering signal is collected by a newly-developed Linear Position-Sensitive Detector (LPSD), which has a count rate capability of at least one million neutrons per second. It enables the Bio-SANS to utilize the full potential of the intense cold neutron source at HFIR. The detector-to-sample distance is adjustable from ~1m to ~15.3m to provide q-range from 0.0009 1/Å to 0.7 1/Å. The data collected at different distances are corrected against dark current, pixel efficiency, sample transmission and geometry to produce 1D profiles to be merged into a full scattering data set. A calibrated standard sample or direct beam intensity is used to obtain the absolutely scaled intensity of protein scattering. A few examples are presented here to demonstrate the procedure and the capability. They include scattering from protein crowded by another protein, membrane protein in a membrane-mimic environment, etc.

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Structural Organization of the Mycobacterial Segrosome

Barnali N. Chaudhuri[1], Shuo Qian[2], Volker S. Urban[2], Rebecca Dean[3].
[1]Faculty of Life Sciences and Biotechnology, South Asian University, New Delhi, India, [2]Center for Structural Molecular Biology, Biology and Soft Matter Division, Oak Ridge National Laboratory, Oak Ridge, TN, USA, [3]State University of New York at Buffalo, Buffalo, NY, USA.

The structural organization of chromosomal partition assembly, which participates in chromosome partition in many bacteria, is poorly characterized. The partition protein ParB spreads on a large segment of DNA encompassing the centromeric *parS* site(s) to form the partition assembly, which is a higher order nucleoprotein complex of unknown nature. The partition assembly interacts with a number of proteins with diverse biological roles such as ParA, SMC proteins and origin tethering factors. We characterized the cross-sectional size parameters and internal organization of the partition assembly using solution X-ray and neutron scattering with hydrogen/deuterium contrast variation. Our data is consistent with a ''DNA outside, protein inside'' mode of partition assembly organization, in which the DNA is wrapping the protein from outside. In addition, we showed that mycobacterial ParA forms apparently ring-shaped polymers *in vitro* by electron microscopy. Based on our data, a testable model of interaction between the ParA polymer and the ParB-DNA partition assembly is proposed.

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The Nucleosome Revisited: Combined Small-Angle X-Ray/Neutron Scattering and Molecular Dynamics Applied to Reconstituted Mononucleosomes

Kushol Gupta[1], Nikolina Sekulic[1], Kathryn Sarachan[2], Joseph E. Curtis[2], Susan Krueger[2], Ben E. Black[1], Gregory D. Van Duyne[1].
[1]Department of Biochemistry & Biophysics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA, [2]NIST Center for Neutron Research, National Institute of Standards and Technology, Gaithersburg, MD, USA.

Nucleosomes are the fundamental structural units of chromatin. A mononucleosome is comprised of 147 base pairs of DNA wrapped around a heterooctameric core of histone proteins that include H2A, H2B, H3, and H4, and other naturally occurring functional variants. In the mid-1970s, the SANS technique was key to the determination of the composition, structure, and conformation of the DNA within this basic unit, fifteen years before the first x-ray diffraction results were available. Small-angle scattering is a long-established technique that is well-suited for the study of macromolecules *in vitro*, as they exist in solution. Small-angle neutron scattering (SANS) is ideally suited to study nucleoprotein complexes, since the neutron scattering strengths of the different macromolecules differ with respect to each other. By employing contrast variation techniques, where the D_2O:H_2O ratio of the solutions is systematically varied, the gross structure and distribution of the individual components of a composite particle can be resolved in a model-independent fashion.

We will present work which revisits these decades-old canonical measurements with a modern perspective. Experimental neutrons from beam line CG-3 at the ORNL High-Flux Isotope Reactor (HFIR) were successfully utilized to study reconstituted mononucleosomes by contrast variation. Our work marries this method with analytical centrifugation and the atomistic modeling approaches implemented in the program SASSIE. This approach allows us to directly reconcile available atomic structures with their solution properties, resulting in complete single and ensemble solution models. As a result of this work, we will present new insights into the distribution of the protein and DNA components of the mononucleosome in solution, including the properties of histone tails in solution and DNA wrapping. The methods presented provide an experimental framework for future examination of variant nucleosome and nucleosome-derived higher order assemblies.

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Conformational Changes of Hsp104 Revealed through Small Angle X-Ray Scattering (SAXS)

Elizabeth A. Sweeny, Kushol Gupta, James Shorter.
University of Pennsylvania, Philadelphia, PA, USA.

Hsp104 is a hexameric AAA+ disaggregase found in yeast. Hsp104 has two key roles in vivo; thermotolerance and the regulation of prions. After thermal or chemical stress Hsp104 has the ability, in collaboration with co-chaperones Hsp40 and Hsp70, to remodel cytosolic aggregates and return proteins to their soluble, native form. Its role in prion regulation is two- fold. In yeast, prions function as non-genetic heritable traits. Hsp104 is required for prion propagation from mother to daughter through nucleation and fiber fragmentation, but cures some prion phenotypes when overexpressed.

Hsp104 is a large, multidomain protein. Each monomer contains two AAA+ domains resulting in an oligomeric species containing 12 sites of ATP hydrolysis. To date, there are no high resolution structures of either monomeric or hexameric Hsp104, and little is known about how the protein changes in shape during the ATPase cycle and how it uses these changes to exert remodeling forces on a variety of substrates.

Here I present ongoing work that uses an in solution technique, SAXS, to study the conformational changes of the Hsp104 hexamer during the ATPase cycle. SAXS studies are well suited to the Hsp104 system due to the large size of the particle, the large available yield after purification, the monodispersity of the hexamer and the large changes that take place in the presence of different nucleotides.

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Slam-Freezing as a Cryopreservation Tool for X-Ray Scattering Study on Membrane Samples

Yimin Mao, Lin Yang.
Brookhaven National Laboratory, Upton, NY, USA.