Summary Panel discussion, 14 September 2018: LINXS workshop Dynamics of membranes and their constituents, 12-14 September 2018, Lund University

Panel:
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State of the Art!

Recent years have seen strong research efforts on the lipid component of biological membranes. While many studies have been focused on membrane structure including curvature, the dynamics aspects are crucial for the function of the membrane including those of membrane bound proteins. The relevant time scales extend from seconds to nanoseconds, and therefore a combination of techniques and modelling tools are required. For kinetic studies "traditional" neutron and x-ray scattering techniques can be used, which make use of stopped-flow set-ups and temperature and pressure jump approaches. In recent years, various inelastic neutron scattering techniques (coherent and incoherent) and X-ray Photon Correlation Spectroscopy (XPCS) have emerged as promising techniques for the study of single molecule dynamics and membrane collective motions. These types of studies will benefit greatly from the new powerful neutron and synchrotron facilities, ESS and Max IV, respectively, that are currently being constructed in Lund. Importantly, computation and sample preparation and characterization are indispensable capabilities needed to maximize the impact of these facilities and these must be in place when ESS and Max IV are completed.

Experimental data alone do not provide the requisite molecular level description of structures and events. In many cases, simulations are needed to provide the critical link that connects scattering data to structure – providing both interpretation and insights that guide subsequent experiments. In this regard, membrane systems have proven enormously challenging for simulation because of the number of atoms involved, the nature of their interactions, and the extended timescale of events inherent to biological membranes (nanosectonds to milliseconds). Successful simulation of membrane systems for interpretation of scattering data therefore requires the leadership-scale computational power, as well as the close interaction between experimentalists and theorists.

It should also be pointed out that unlike electron and x-ray scattering, neutron scattering can distinguish between hydrogen (H) and its stable isotope deuterium (D). Of the major classes of biomolecules (lipids, proteins, nucleic acids and carbohydrates), membrane lipids are the richest in hydrogen. They can thus be readily detected and easily distinguished from other classes of biomolecules. For example, selective H/D isotopic labeling of lipids can generate contrast between laterally segregated components and obviates the need for chemical labels and their associated artifacts. In short, H/D isotopic labeling provides dramatic improvements in sensitivity and selectivity in scattering experiments and enables studies that would otherwise be impossible in the absence of this capability.

Increasingly, synchrotron and neutron user facilities have come to the realization that there is increasing value in having sample preparation and characterization facilities that include light scattering Langmuir-Blodgett troughs, NMR, fluorescence microscopies, and surface characterization techniques (e.g., AFM). These capabilities not only allow for better planning of experiments at the large-scale facilities, but also provide complementary information that is usually essential for the evaluation and support of neutron and synchrotron x-ray and neutron data.

Challenges

We must identify grand challenges rather than convenient problems that can be easily be solved with neutrons and x-rays. This includes coming up with scientific opportunities that grabs the attention of biologists. Here is a list of problems that were discussed:

1. While it has been amply demonstrated that NMR and Neutrons are powerful to reveal dynamic aspect of membranes, the potential of x-ray techniques like XPCS is not full exploited in this context.
2. How can we co-refine and model data in the dynamic domain recorded with x-rays, neutrons and other techniques like NMR.
3. To reveal the dynamics of interfaces that also includes reactions and propagation of structure. The relation between structure and dynamics for more complex and biomimetic systems.
4. Dynamics of transition require knowledge of structure. The challenges are to be able to establish maps of structures on different time scales and to unify the structural and dynamical description of biological systems.
5. To obtain and formulate more biologically relevant lipid species that address the true complexity and diversity of lipid membranes.
6. How do we look at living systems? Cancer cells versus normal cells? The limitations of the technique make interpretation of data from living system a true challenge! For instance how do we account for and investigate the effects of the cytoskeleton.
7. How do we create a sample environment that allows us to use the tool box that molecular biologists have developed?
8. Establish close collaboration between experimentalists and simulators not only for structure, but also for dynamics!
9. Design the right experiments to reveal the dynamics, which in turn requires that one identifies the techniques that is best suited rather than squeeze everything into classical scattering techniques.
10. How to translate results from model experiments using vesicle fusion into potential cellular processes and how relate that to cell function.
11. For new scattering infrastructures being built up the challenge is to create a community of users that can start with relevant and important experiments on day one, rather than calling in friendly users.

Needs

Instrumentation:

During the initial phase of ESS operation SANS, Reflectometry, Neutron Spectroscopy and the diffraction instruments will be available and these instruments can be used to address some aspect of neutron dynamics. However, there are clearly gaps in the instrumental suite, in particular:

- No Spin Echo instrument is currently in the works during the initial suit of instruments at ESS. This was considered to be a severe shortcoming for this scientific community. ESS is currently preparing a capability gap document, so the community needs to stress and argue for the need of instrument like the Spin Echo one.
- Regarding x-ray instrumentation, current XPCS instruments are able to catch dynamics on the microsecond time scale. There is need to develop such x-ray instrument for nanosecond time scale dynamics, which will require the development of new detectors. It poses a challenge to obtain detectors that operates on the 10 kHz time scale.
- Grazing angle neutron scattering and Spin Echo Spectroscopy (GINSES) are specially suited for biomembrane studies both in terms of structure and dynamics. These techniques are specially in need of a bright source and therefore should be developed at the ESS.

Modeling:
We need to be able to address the difference in time scale between simulation and experiment. We also need to be able to make use of additional time resolved data from other techniques in combination with neutron/x-ray data.

Promoting integration between biophysics and medical and clinical sciences.
The grand challenges in health and life sciences require research on different length scales and time scales.

- We need to address the fact that a living cell is never at equilibrium. This requires fundamental biophysics studies with integration of medical faculty competence and resources to conduct clinically relevant research.
- Understand how multi-domain and multicomponent molecular complexes are assembled and regulated during life processes, not only in terms of structure but also in view of the relevant dynamic processes and time scales involved.
- Establish advanced deuteration and sample preparation expertise and facilities is particularly important for life science studies
- Understand natural bilayer membrane structure and dynamics, fusion, and vesicle, pore, and domain formation. Understand the structural and functional interplay between membranes and other molecules; membrane protein folding, structure and function; perturbation of membranes in disease
- The development of new therapeutic strategies requires a deeper and fundamental understanding of the interaction between man made particles and living cells, not only structural changes but also the dynamics. Such knowledge is essential for designing new drugs for human disease targets that have better target specificity, improved binding, and that are not susceptible to drug resistance.
- Neither x-rays and neutrons alone can do everything, and thus combinations of the two as well as with other techniques is key to advance the field. Here it would be useful to establish common labs for ESS and MAX IV like the successful partnership for soft and condensed matter (PSCM) at ILL/ESRF in Grenoble. Such a lab will also foster the collaboration between the neutron and x-ray community as well as between ESS and Max IV to efficiently use available resources.

Personal Resources:

ESS and Max IV provide a unique opportunity to attract outstanding researchers to the region. This needs to be utilized by Lund University as well as Malmö and Copenhagen Universities to create Lecture/professor positions at the universities. Do not miss the opportunity! This happened elsewhere. A good example is NCNR at NIST in Gaithersburg, which have a very fruitful collaboration with University of Maryland and University of Delaware.

How can LINXS help?
Linxs will be able to host 50-90 scientists when operating with its planned budget. While the LINXS is not intended to have its own labs, it can act as a bricks and mortar place to get scientist to work on important problems and challenges that require an interdisciplinary net-work of researchers. Other activities beyond conference organization are:

- Being an opening door for new users of neutron and x-ray for the advancement of science in emerging fields likes dynamics of membranes and their constituents.
- Foster communication between the x-ray and neutron community.
- Share and promote efficient utilization of resources.
- Policy issues in the form of e.g. taking the lead on producing white papers on different topics related to neutron/x-ray science.
- Possibility to fund local salaries and invitations for prominent researcher that can promote neutron and x-ray studies for the Swedish and international research community.
- Expand community awareness of the advantages of neutron and x-ray scattering and recruit the biology community to the neutron that are available today and point to the possibilities that ESS and MAX IV will offer in the future.
- Create an inter-disciplinary network and bring together complementary technique.
- Aid the communication process between the academic institutions and MAXIV/ESS.