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CONTENT

WHERE NUCLEAR PHYSICS APPLIES TO BIOSCIENCES

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INTRODUCTION

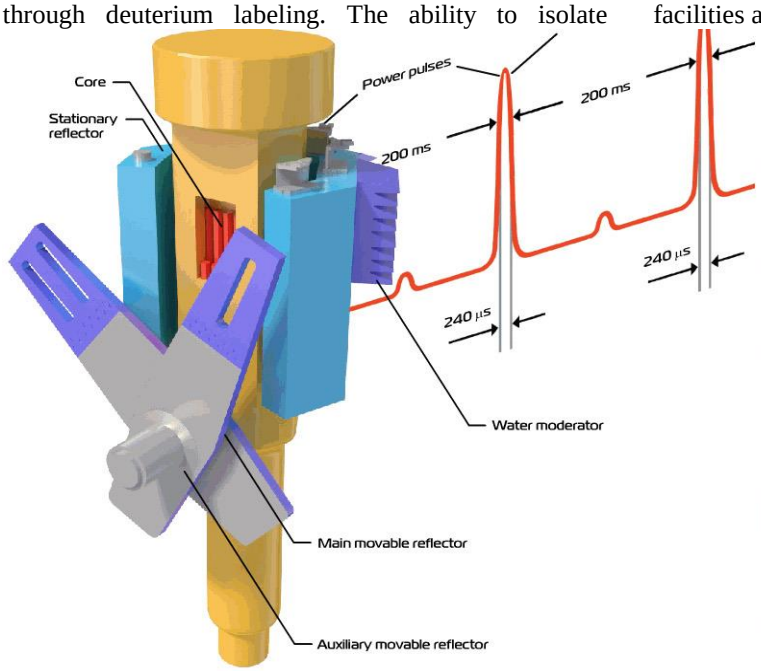
Biological membrane mimetics, such as liposomes, lipid bilayers and model membranes, are used in a broad range of scientific and technological applications due to the unique physical properties of these amphiphilic aggregates. They serve as platforms for studying the soft matter physics of membranes and membrane dynamics, interactions of bilayers with drugs or DNA, and effects of various additives or environmental changes. The modern state-of-the-art research takes advantage of joining brilliance of X-ray scattering sources with some peculiar properties of neutrons, and combines results with the power of computer simulations. The advances in chemistry, and deuteration possibilities in particular, allow for better experimental spatial resolution and possibility to pin-point labels within membranes. It is only a matter of time for many biological functions that occur at the membrane interface to be matched with the structural properties of these membranes.

The experimental technique of scattering should be pointed out with regards to the structural biology. Scattering techniques, especially those of X-rays, have traditionally been used to determine the structure of 3D crystals on atomic levels. However, advances achieved over past decades developed to an extent that scattering approaches can successfully characterize the physical properties of disordered materials such as biomimetic membranes. The X-ray and neutron scattering methods are now applied to elucidate the material properties previously thought to be the domain of other techniques, and even provide possibilities not present in any other methods. In particular, neutron diffraction can determine the distribution of water or individual components through deuterium labeling. The ability to isolate individual molecular groups at atomic level of detail is unique among biophysical techniques. Furthermore, discovery of the center of mass distribution of a chemical group is information directly comparable to molecular model simulations.[1]

NEUTRON SOURCES

The discovery of neutron in 1932 by English physicist James Chadwick[2] started an era of neutron scattering. Its properties and advantages for condensed matter research were recognized quickly, while creating a need for the sources of these *mysterious* particles. The two nuclear reactions in which neutrons are produced were described soon after. The relatively more accessible fission became utilized in nuclear reactors, which however provide a low efficiency outcome and are becoming publicly unpopular due to several nuclear disasters. More promising then appears to be spallation sources that do not require dangerous fissile material, and provide much higher efficiency due to the nuclear spallation reaction and also due to the pulsed nature of such sources. Their disadvantage on the other hand is an involvement of highly sophisticated and complex systems, relevant of course to the construction cost.

In addition to the two above mentioned neutron sources spread widely around the world, there is a third type combining the advantages of both. The pulsed fast reactor (IBR)[3] constructed in Dubna, Russia was designed to take advantage of relatively simple and energetically inexpensive nuclear fission reaction. The wide range of neutron wavelengths combined with time-of-flight method then allows increasing the facility efficiency to and above the most modern neutron facilities around the world.[4]



Average power, MW	2
Burst power, MW	1850
Fuel	PuO_2
Number of fuel assemblies	69
Maximum burnup, %	9
Pulse repetition rate, Hz	5; 10
Pulse half-width, μs: fast neutrons thermal neutrons	 240 320
Rotation rate, rev/min: main reflector auxiliary reflector	 600 300
MMR and AMR material	nickel + steel
MR service life, hours	55000
Background, %	7.5
Thermal neutron flux density from the surface of the moderator*: - time average - burst maximum	 ~10^{13} n/cm²·s ~10^{16} n/cm²·s

* More precise data on the thermal neutron flux density after the modernization will be available when the reactor operates at full power.

Figure 1: Design and parameters of high-flux pulsed reactor IBR-2M.[4]

BIOMIMETIC SYSTEMS

Owing to Clifford G. Shull and Bertram N. Brockhouse who developed neutron scattering techniques for studies of condensed matter,[5] the interest in neutron scattering on biologically related soft matter systems received an increased attention. Structural studies of lipid membranes and their changes due to the environmental and compositional changes, affected by cholesterol in particular, fell in a focus from the very beginning. The thickening of lipid bilayers upon the addition of cholesterol has been observed in various lipid systems. However perhaps more interesting are the recent results on the location of cholesterol in membranes of various lipid composition. In contrast to ordered bilayer composed of saturated lipids (e.g., DMPC) or those of a small degree of unsaturation (e.g., POPC), were cholesterol adopts its canonical orientation parallel with lipid chains, more disordered bilayers containing polyunsaturated fatty acids (PUFA) orient cholesterol parallel to the bilayer plane.[6]

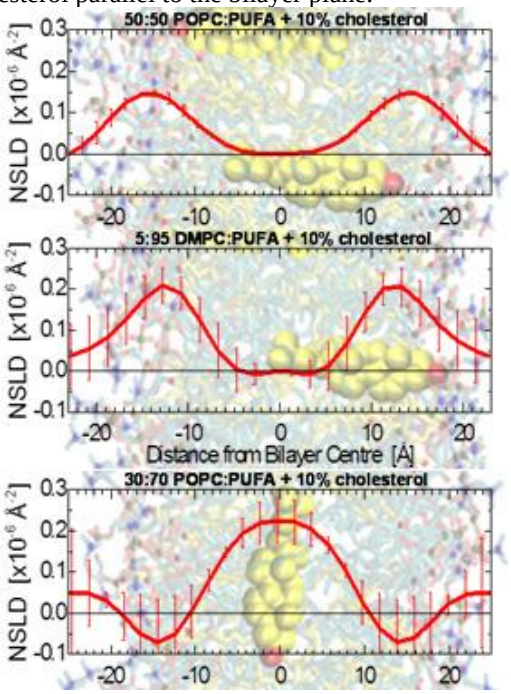


Figure 2: Neutron diffraction results revealed the location of the cholesterol's labelled head outside the hydrophobic region of more saturated bilayers (top and middle panels), while in the center of polyunsaturated bilayers (bottom panel). Adopted from Ref. 6.

The significance of the preference of cholesterol for different lipids may also be rationalized in terms of what we presently know of biological systems. For example, in plasma membranes saturated lipids are primarily located in the outer monolayer whereas unsaturated phospholipids are more abundant in the inner leaflet. By pushing cholesterol to the center of the membrane, a PUFA-rich domain on one side would enhance the transfer of the sterol to a lipid raft on the other. It is even possible to imagine this mechanism resulting in the formation of functionalised domains that could facilitate biosynthetic pathways of cholesterol and its transport to and from cells.[6]

The cell membrane plays an important role also in the molecular mechanism of Alzheimer's disease (AD). Its chemical composition and the incorporation of cholesterol have been linked to increased amyloid toxicity, while melatonin has been shown to have a protective role. Although the underlying molecular mechanism is not well understood, recent results of neutron diffraction shine some light on the membrane's structural properties. Both the experimental and theoretical data show that the effect of melatonin on bilayer properties is opposite to that of cholesterol, which has the ordering effect. In contrast, melatonin decreases the order and thus inducing the increased fluidity in the model membrane.[7]

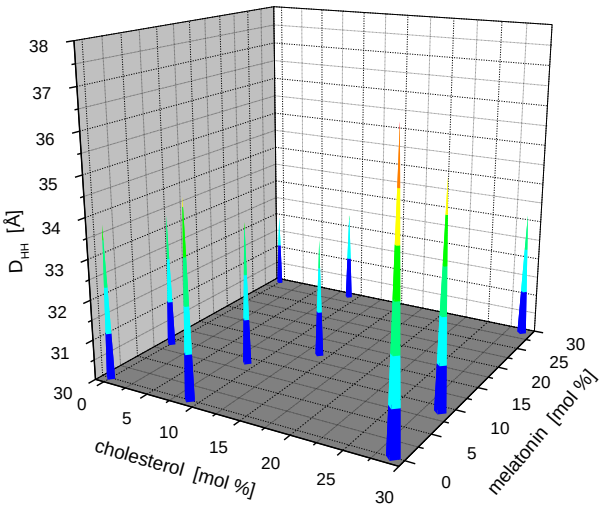


Figure 3: Bilayer thickness D_{HH} as a function of cholesterol and/or melatonin concentration reveals the thickening effect of cholesterol while the opposing effect is caused by the addition of melatonin.

CONCLUSIONS

Neutron scattering proves its ability to support bio-relevant studies with data not accessible to other techniques. In particular, the specific deuteration and contrast variation techniques can reveal even subtle details. Most importantly, such structural studies help to further our understanding of critical biological process taking place in biomembranes.

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