

Drug delivery

Moving membranes and molecular elevators

Maikel Rheinstädter

Inelastic neutron scattering experiments are uncovering how the subtle dynamics of lipid bilayers are affected by small molecules. The results could lead to a better understanding of the role of drug enhancers in medications.

Biological membranes play a crucial role in living processes, protecting cellular contents from the exterior environment, and controlling the transport of materials in and out of the cell. They are composed of a bilayer of self-assembled phospholipids, which each have a hydrophilic phosphate ‘head’ and two hydrophobic hydrocarbon ‘tails’, arranged so that the water-loving heads are facing outwards, sandwiching the tail region. Also embedded in the bilayer are various other molecules including proteins with specific functions that mediate much of the cell’s activity.

For the past 40 years, the fluid mosaic model has provided the textbook description of this membrane as a largely passive two-dimensional, liquid or gel-like barrier through which materials can diffuse. However, research is gradually revealing that the structure, composition, and the wave-like elastic motions of the lipid bilayer itself, mediate the protein interactions, and are probably influential in the transport of small molecules – for example, drugs – into the cell. For example, the attachment of short-chain alcohols such as ethanol onto the head-group region of the bilayer is known to increase the fluidity and disorder of the membrane, and so increase its permeability. The presence of alcohol can thus increase the effect of a prescribed drug.

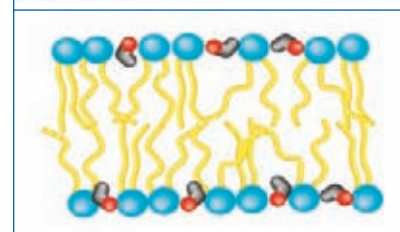
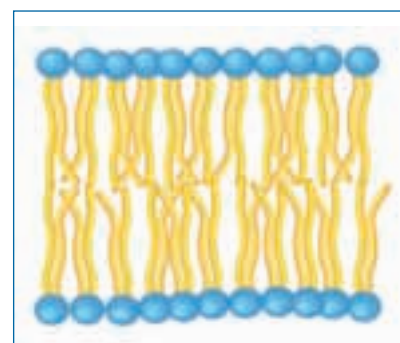
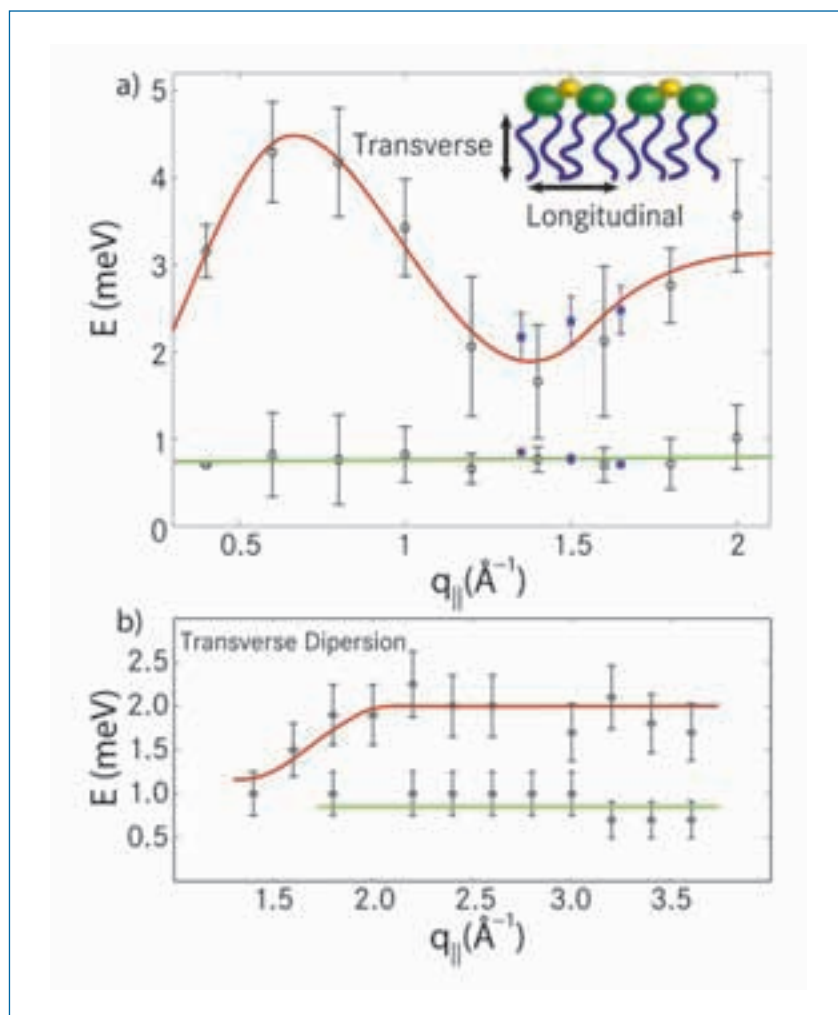
Recently, we used inelastic neutron scattering to investigate in more detail how ethanol affects the behaviour of a lipid bilayer. By reflecting low-energy neutrons from supported model membranes, we were able to measure and analyse the small changes in energies associated with collective fluctuations in the membrane on a timescale of only 100 picoseconds.

The samples were prepared as highly oriented stacks of 1,2-dimyristoyl-sn-

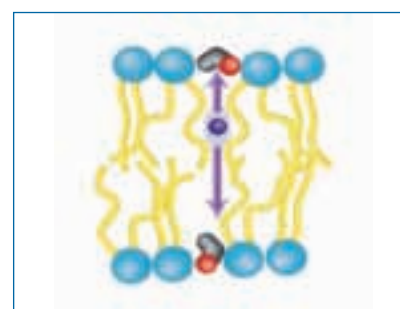
glycero-3-phosphatidylcholine (DMPC-d54) bilayers with deuterated hydrocarbon tails to increase contrast, and spread out on silicon wafers. Stabilised layers with 5% ethanol were also prepared, to give a structure whereby each lipid molecule had an alcohol molecule attached. Using IN12, the cold-neutron triple-axis spectrometer operated by JCNS at the ILL, in conjunction with a vertically positioned analyser, we measured the inelastic



IN12



A graphic of a lipid membrane with and without alcohol.



A graphic of a lipid membrane with and without alcohol.

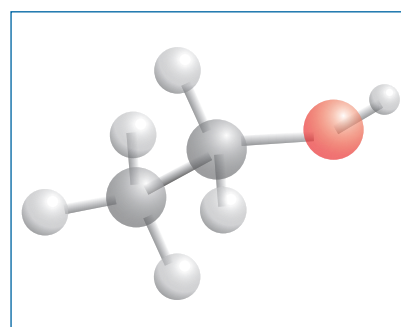
reflections at various energies and angles from the membrane, with and without the presence of ethanol. Computer simulations of molecular dynamics were used to interpret the results.

A new dynamic mode

As seen previously, the inelastic measurements revealed a collective acoustic ripple going across the pure lipid membrane. When ethanol was present, however, there was an additional low-energy mode that appeared to originate from a vertical movement traversing the membrane, which was associated with the lipid chains. We interpret this as coherent vertical waves passing up the tails. This scenario is supported by the diffraction data, which showed that the area occupied by each lipid molecule increased by about 4% in the presence of ethanol, so that the tails are less well packed.

These results may explain how ethanol and other small molecules such as aspirin

act as drug enhancers. They may enable active transport across membranes, by creating a series of travelling voids and kinks in the tails that zig-zag up through the membrane and act as molecular elevators for drug molecules, thus allowing them to enter the cell more easily. We are now investigating the possibly similar role of aspirin to obtain a better understanding of the drug-delivery process into the cell at a molecular level. ■



The structure of ethyl alcohol.

Maikel Rheinstädter

is an Assistant Professor in the Department of Physics and Astronomy at McMaster University, ON, Canada. He is also affiliated with the Canadian Neutron Beam Centre at Chalk River, ON, Canada. Before moving to the US and Canada, Dr. Rheinstädter worked as a post-doctoral researcher with JCNS at the ILL in Grenoble.

References

“Ethanol enhances collective dynamics of lipid membranes”, Martin D. Kaye et al., Phys. Rev. E, 2011, 83, 050907(R).